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BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles by

BARTON CHILDS

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THE DIAGNOSIS AND MANAGEMENT OF ENDOMETRIOSIS

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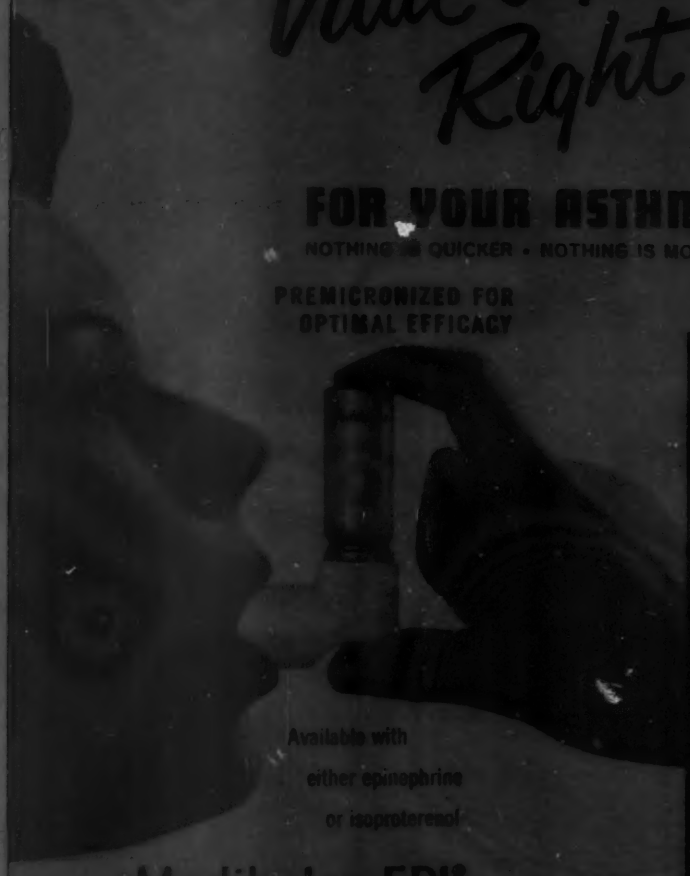

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*L. O. Randall and J. Selitto, *J. Am. Pharm. Assn. (Sc. Ed.)*, 47:313, 1958.

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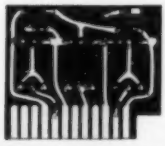

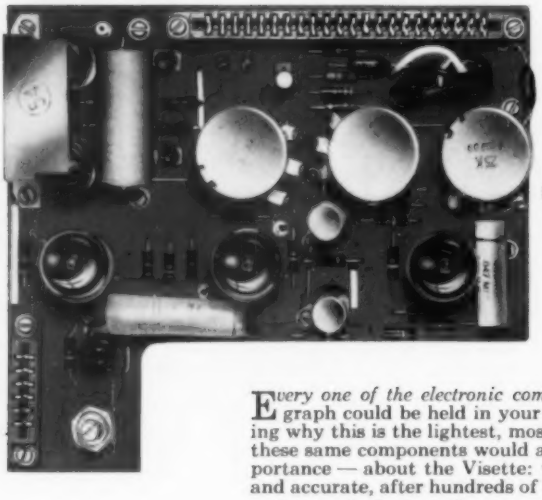

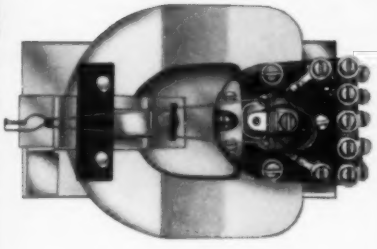

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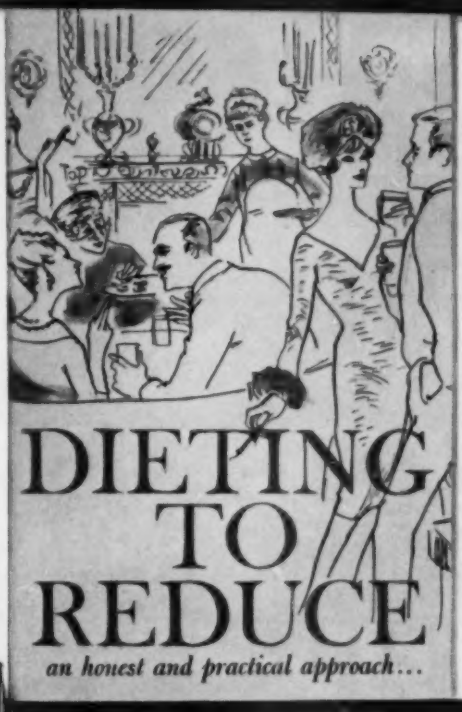

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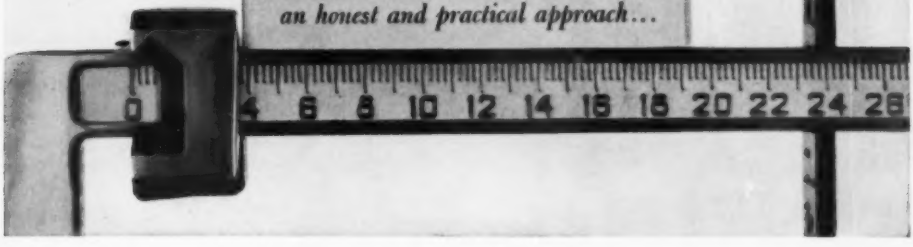

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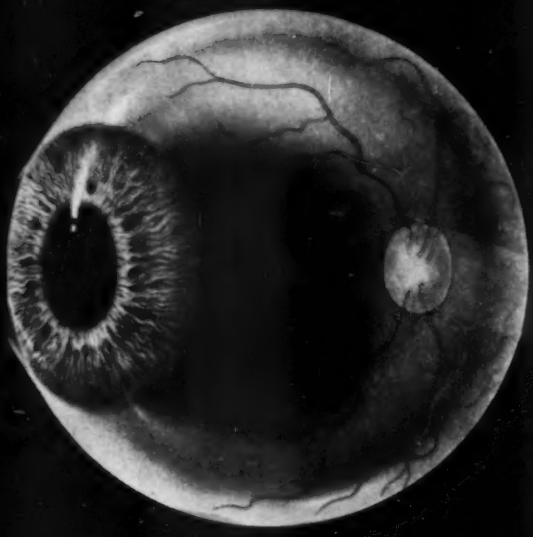

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Reinhardt, D. J.:
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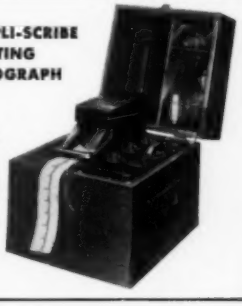

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[1] Thomas, M. H., in Green, J. R., & Steelman, H. F.: Epileptic Seizures, Baltimore, The Williams & Wilkins Company, 1956, p. 57.

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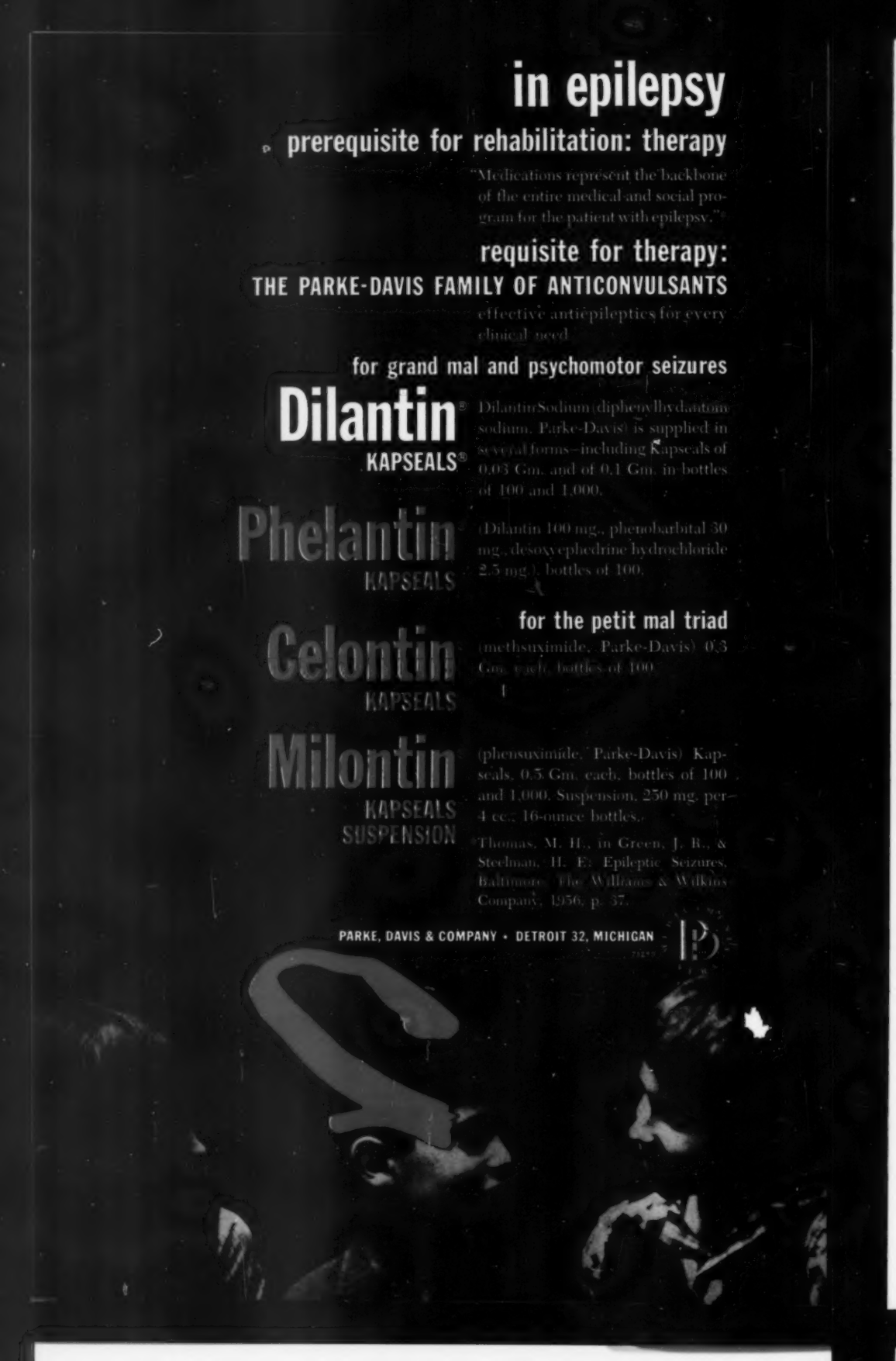

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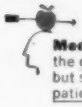

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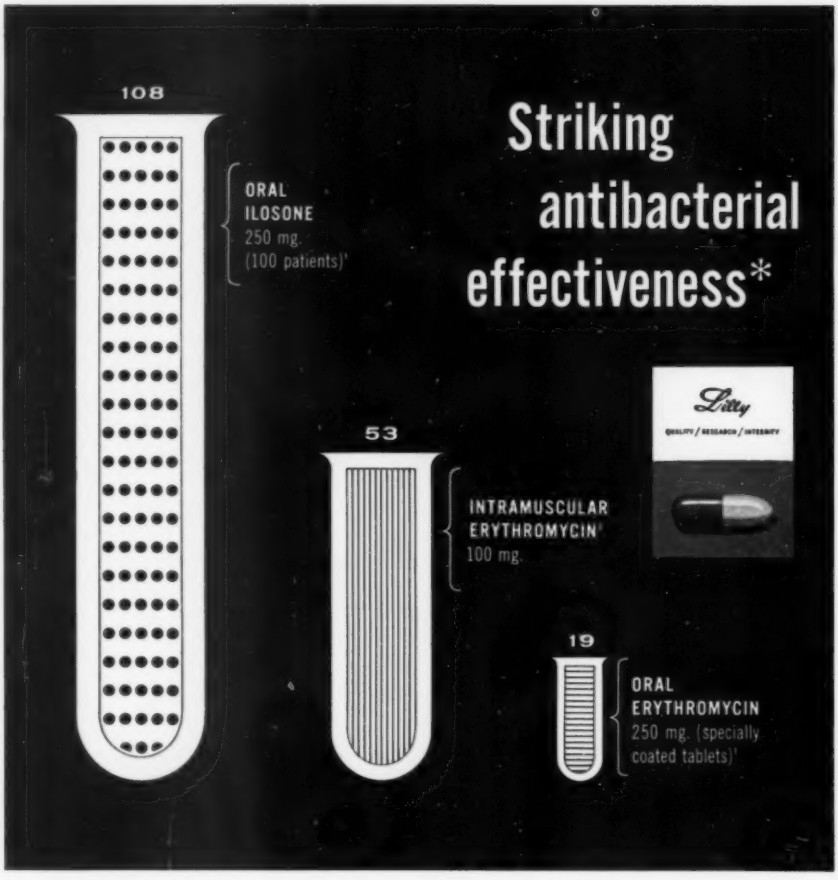

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1. Griffith, R. S., *et al.:* Antibiotic Med. & Clin. Therapy, *5*:609 (October), 1958. Note: Peak levels with the oral erythromycin tablets (thirty-three dilutions) were not observed until four hours after administration. 2. Data from Griffith, R. S.: Antibiotics Annual, p. 269, 1954-1955.

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

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BULLETIN OF
THE NEW YORK ACADEMY
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VOL. 35, NO. 2 FEBRUARY 1959

HEREDITARY ASPECTS OF DISEASE*

BARTON CHILDS

Associate Professor of Pediatrics
Johns Hopkins University School of Medicine
Baltimore, Maryland

GENETICS is the study of heritable variation. The genetic constitution possessed by an individual provides him with a long list of potentialities which are or are not realized, depending upon the kinds of environment in which it is called upon to function. The genes responsible for disease are no different from those determining other forms of variation, and must also function in similar environmental circumstances. Thus a particular variation, whether it be disease or not, is caused by a particular gene operating in a favorable environment, and a change in either component will alter it. For example, a person who does not possess the gene causing galactosemia will not have that disease, but equally such a gene would probably remain one of the secrets of nature in a society which did not use milk. I stress this point at the outset because to ameliorate genetically determined disease, the physician must so alter the metabolic environment as to render the effects of the deleterious gene harmless, and in order to know whether or not this is possible he must know how the gene acts.

* Presented at the Second Annual Postgraduate Week at The New York Academy of Medicine, October 14, 1958.
Original work reported herein was supported by a grant from The National Heart Institute, National Institutes of Health, Bethesda, Maryland.

We speak of genes as if we knew what they were, when in fact our knowledge on this point is imprecise. We can detect the presence of a gene only when it exists in two or more alternative forms reflecting themselves as two or more variants of a characteristic in a population, and segregating in families according to Mendelian laws. This suggests the particulate nature of genes. We know also that the chromosomes, in which the genetic material resides, have a linear topography so that each gene occupies an allotted locus. A sexually reproducing organism will have in each cell two homologous chromosome sets, and the homologous loci in these chromosomes may be occupied by two representatives of the genetic material which are identical, or by two which differ one from the other. If identical, we say the cell and individual are homozygous; if different, heterozygous. It is possible for genes occupying homologous loci to be different because of mutation; presumably a change in the genetic material has occurred during replication. Such a change is then reflected in some alteration in the metabolism of the cell, creating thereby a new variant of a particular characteristic; a new phenotype. From this we may infer that though a given locus may be occupied by different genes, all the genes at that locus are concerned with the same function. Thus a gene may be defined as a unit of mutation and a unit of function. We may make a further definition. At meiosis, during the formation of the germ cells, the homologous chromosomes intertwine and parts of each may cross over and interchange with the other, so that what segregates into the zygote is a unique chromosome with new combinations of genes. Since the points of breakage and crossing over appear to be random, we may define a gene as the smallest unit of the genetic material which cannot be broken by crossing over. The most recent evidence suggests that these three units are not the same, but that a larger functional unit contains many smaller units of mutation and of crossing over[1].

These definitions are based upon observations made by classical genetic techniques, and while they have revealed a definite intra-chromosomal organization, they do not tell us in physico-chemical terms what a gene is, nor what it does. To these questions the biochemists and physical chemists are in the process of giving us the answers[2, 3, 4]. We now know that an important component of the genetic material is deoxyribonucleic acid (DNA) and that this material consists of long strands of connected nucleotides, each of the latter containing one of four purine

or pyrimidine bases. Such a structure implies that the codification of the information inherent in the genetic material consists of the kinds of sequential arrangement of the four different nucleotides. Thus a gene may be defined in part as some sort of segment of DNA consisting of a series of nucleotides arranged in a specific way. We cannot be concerned here with the speculations which attempt to define the mode of transmission of the genetic information to the remainder of the cell, but it is apparent that genetic control of cellular metabolism is mediated by the influence of the genetic material upon the construction of proteins. Though we do not know precisely by what means, it seems likely that each gene locus bears a functional relationship to some protein molecule, and that at least some aspect of the specificity of that protein is determined by the particular occupant of that locus. One might like to think that the arrangement of nucleotides within the DNA is reflected in the sequences of amino acids in the proteins, but this hypothesis has not been proved. But whether the affinity between gene and protein is a direct one, or is achieved in some indirect or roundabout way, each gene has a single function, and that function is mediated by a protein. Enzymes are proteins and have as their function the control over reaction rates. Thus we may make a final definition of genes as units of the genetic material which control the specificity of the cell proteins, and ultimately the balance of metabolic reaction rates[4].

But what of the genetic variants and diseases which confront the physician? It is reasonable to assume that every gene operates in the way just described whether its ultimate phenotypic effect is a morphological variation, a defect in renal tubular reabsorption or an abnormal hemoglobin. Unfortunately, however, we are seldom able to see and measure gene action so clearly. Most commonly, genetic etiology is suggested by familial aggregations of persons showing some obvious variation, and we speak of gene action only in terms of a description of the characteristic itself. This is a little like standing on a mountain top and observing an adjacent peak which appears to be very close. But to reach the latter there is a long descent into the valley below, passage through an impenetrable forest, a river to ford and then a long, arduous ascent, covering in all a distance many times greater than that between the two peaks which seemed so near. The point is that there are many levels of gene action, and what we can say that a gene does in a particular instance is only to cause an effect which we can detect and

measure with the techniques at our disposal. The most fundamental level, of course, would be an assessment of the gene itself, but this at the moment is impossible. More likely is a measurement at the level of what we may regard for practical purposes as the gene product; that is, a measurement of some physical or chemical properties of the protein molecule bearing the most direct affinity to the gene in question. This has been seldom possible but doubtless will be a more popular approach in the future. We do, however, have examples of this in the blood group antigens and the hemoglobin variants. Antigen specificity is a reflection of structure and configuration and is certainly related to gene specificity. Genes occupying at least one locus concerned with hemoglobin formation may be distinguished by variations in electrophoretic mobility and solubility; and the relationship of genes to protein structure has been brilliantly demonstrated quite recently by Hunt and Ingram[5], who have shown that hemoglobins S and C differ from hemoglobin A only by the substitution of valine and lysine respectively for one glutamic acid, in the sequence of amino acids of these proteins. Mutation at this locus has resulted in alteration of only one of about 300 amino acids, and all else is presumed to follow from this seemingly insignificant change.

Since we have seldom been able to describe the molecules themselves, we must be content more commonly with measurements of some aspect of their physiological activity. Enzyme systems lend themselves most readily to this kind of assessment, since they control reaction rates and we may measure the presence or absence or rate of appearance of a reaction product. This has been done in a number of genetically determined variations and diseases, and enzyme activity has been found to be unmeasureable or reduced. It is important to realize that this kind of measurement does not say necessarily that the enzyme protein is absent or present in reduced concentration, but may equally imply that its specificity has been altered so that it no longer functions with optimal activity. Normal enzyme may be present in normal concentration, but be inhibited; or the concentrations of substrates or cofactors, themselves sometimes under genetic control, may be reduced. Indeed, it may be difficult to assign primary responsibility for reaction failure to the appropriate gene. A good case in point is a newly discovered variation in erythrocytes studied by Beutler, Dern, Alving[6] and others in Chicago, in which the red cells of susceptible persons are found to hemolyse readily in the presence of primaquine, acetyl phenylhydrazine,

sulfanilamide and other substances. These cells were found to show a marked instability of reduced glutathione (GSH) after in-vitro incubation with some of the drugs mentioned, reflected by a very marked drop in red cell GSH[7]. In an attempt to discover an enzyme basis for this defect, Carson, Flanagan, Ickes and Alving[8] examined the activity of glutathione reductase, an enzyme responsible for the maintenance of glutathione in the reduced state. This enzyme was normally active, but when they considered reduced triphosphopyridine nucleotide, a cofactor involved in this reaction, they discovered that inadequate amounts of this substance were being supplied because of failure of a coupled reaction which generates it. The activity of the enzyme glucose-6-P dehydrogenase which controls the rate of oxidation of glucose-6-P was found to be low, depriving therefore the first reaction of a necessary metabolite. Thus at this level the problem has already become more complex; and in general it may be said that the more proximal to the gene action that one can make a measurement, the less will be the variability; while more distal functions are more readily modifiable by other genetic or environmental factors.

The living cell must be considered as a multiphase system in a dynamic state in which reactions are coupled, sequential, or otherwise interdependent, so that reaction failure at one point must lead to alteration of reaction rates elsewhere. This, then, constitutes a third phenotypic level. Here the type and scope of secondary and tertiary reactions consequent upon primary reaction failure will depend upon the nature of the primary system, its strategic importance in the economy of the cell and the extent of its abnormality, together with the capability of the organism to remedy the defect by other means and to deal with accumulated intermediates. These latter may be toxic to the organism, altering other reaction rates by competing for enzymes or by other forms of inhibition. An excellent example of this has recently been given by Sidbury[9], who showed that galactose-1-P which accumulates in the tissues of patients with galactosemia inhibits the action of phosphoglucomutase, the enzyme responsible for the conversion of glucose-1-P to glucose-6-P.

The final phenotypic level which constitutes a description of the characteristic or the illness is a composite of all effects, and here again, genetic and non-genetic factors increase the variability, acting as the background against which the effects stemming from the primary reac-

tion are to be seen. It must be recognized that this scheme of phenotypic levels is entirely arbitrary, but it might be useful in sorting out the complexities of the action of genes.

In the beginning, geneticists were principally concerned with morphological variations, and gene action was related directly to the characteristic being studied. A terminology based upon sound genetic principles came into being and remains useful today, but it does not always reflect the more penetrating understanding of gene action now current. Any rapidly developing discipline has its own semantics, and genetics is no exception. I would like, therefore, to examine one or two of the principal terms and to discuss their meaning in the light of modern concepts.

Chief among these is dominance. A fully dominant gene is one which expresses itself equally well in both heterozygote and homozygote, and a recessive gene is one which expresses itself only in the homozygous state. In the case of morphological defects (which are, in fact, a reflection of the biochemical events of embryogenesis), this might seem a satisfying description of the functional properties of the gene. But when we consider conditions amenable to biochemical examination, we see that our description of gene action depends upon what measurements we make. There is perhaps no better example to cite than that given by the genes at the hemoglobin locus. If we consider sickle cell disease alone, the distribution of this characteristic in families suggests a recessive gene; that is, all affected will usually appear in one generation. If we consider sickle cell *trait* alone, the distribution is that of a dominant gene, while consideration of both trait and disease together suggests a gene showing incomplete dominance; that is, exhibiting a more extreme effect in the homozygote than in the heterozygote. But hemoglobin electrophoresis reveals no dominance at all; in the heterozygote the product of both genes, hemoglobins A and S, are present together. Perhaps if we were able to detect them, all genes would be found to manifest some expression, and dominance could be seen as something which has no qualitative relationship to gene action, but which depends upon the means used to find and measure that action.

Hunting for heterozygous expressions of recessive genes is a popular pastime just now. We have recently been dealing with some families containing patients with familial non-hemolytic jaundice[10]. The distribution of cases in families suggests segregation of a recessive gene,

and there is evidence that the defect in such patients is one of making an excretable glucuronic acid conjugate of bilirubin[11]. Because of this, bilirubin accumulates and the patient is always jaundiced. Parents and sibs, however, are neither jaundiced, nor show any hyperbilirubinemia. Our studies, in which we administered substances other than bilirubin and measured the amounts of the conjugates which appeared in the urine, showed that parents, some sibs and some grandparents exhibited a capacity to manufacture glucuronic acid conjugates of the test substances greater than that of the affected patients but less than that of the normal controls. Thus with respect to jaundice this gene is fully recessive, but with respect to glucuronic acid conjugation of test substances, it shows partial dominance.

There is now an ever increasing list of conditions due to "recessive" genes, manifesting some effect that may be found in the heterozygote[12]. Indeed we may look forward to a time when all such recessive genes will be found to exhibit some detectable effect in heterozygotes.

Before leaving dominance I would like to point out that the frequency of most of the conditions caused by so-called dominant genes is such that we seldom see the homozygote and so cannot be sure whether or not the genes are fully dominant, though we might expect the homozygous effect to be more severe. For example, if the incidence of a disease due to a dominant gene is 1/1000, the frequency of homozygotes would be 1/4,000,000, and if the disease incidence is 1/50,000, there would be only one homozygote in the world. Conversely, the ratio of heterozygotes to homozygotes is such that given a disease due to a recessive gene and with a frequency of 1/10,000, 2 per cent of the population would be carriers. Thus many such "deleterious" genes exist in the genotypes of healthy persons, and make their contribution to normal variability.

A gene whose effect is undetectable is said to be impenetrant, and families are described in which a characteristic due to such a gene appears to skip a generation. That is, someone marked as the possessor of the gene because he is in the direct line of passage has not shown the characteristic. But like dominance, the penetrance or impenetrance of a gene is determined by success or failure in the detection and measurement of one or other of many parameters. Failure may be associated with the use of insufficiently sensitive techniques, or it may be that the gene effect is detectable only in the presence of some special environ-

mental condition. For example, the heterozygous carrier of the gene for galactosemia appears on physical examination to be normal in every way, and the usual laboratory tests are equally unrewarding. But, after giving a load of galactose to such carriers, Holzel and Komrower[13] showed that a defect could be brought out: that is, the galactose tolerance was abnormal. Here the abnormal enzyme system has been artificially taxed, and a measureable effect stimulated. But of eleven parents tested in this way, four showed a normal tolerance to galactose, so that under these conditions the gene is only partially penetrant. Estimation of the activity of the enzyme phospho-galactose-uridyl transferase, the deficient enzyme, was carried out by more direct means on the erythrocytes of heterozygotes by Kalckar, Anderson, Kurahashi, and Isselbacher[14], but the discrimination between the heterozygotes and normal persons was even more imperfect. A new method reported by Kirkman and Bynum[15], in which a different reflection of enzyme activity in the red cells is measured, has, on the other hand, shown nearly complete discrimination. So, depending upon whether or not the enzyme system is put under stress, or depending upon which technique is chosen to measure activity, the penetrance of the gene in heterozygotes varies widely.

Sometimes in certain circumstances a gene may be so impenetrant as to leave us unaware of its existence. I refer again to the primiquine sensitive red cell variant previously mentioned. Among the substances capable of causing hemolysis of susceptible cells are the metabolites of naphthalene[16]. Young children sometimes ingest moth balls, which consist of naphthalene, and in some instances hemolytic anemia and jaundice ensue. Figure 1 shows a pedigree of the family of an infant who suffered such an episode. The child was a one day old infant and was the only member of the family who was ill in this manner. A diligent and imaginative medical student asked the mother if she had been eating moth balls, and to his surprise received an affirmative answer. She had in fact been indulging this peculiar appetite during the last trimester of her pregnancy and had apparently transmitted the metabolites of naphthalene to her baby through the placenta. Subsequent examination of the mother's blood revealed that she had a mild hemolytic anemia. Now this susceptibility is genetically determined and it was possible by appropriate techniques to detect it in relatives who had never been anemic and who had certainly never dined on moth balls. Here the gene,

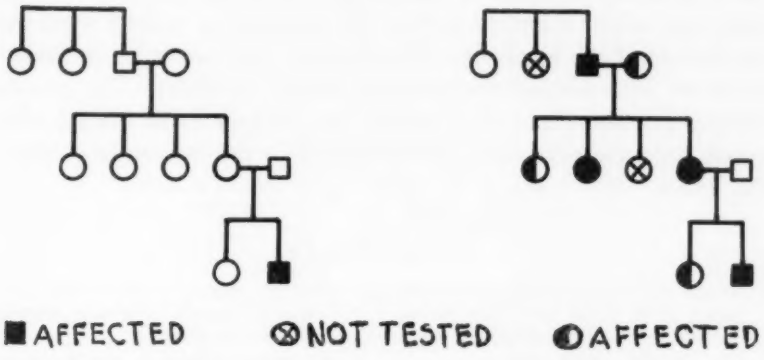

Fig. 1. Family tree of patient who suffered naphthalene poisoning.
Left: expression of gene in family with respect to anemia and jaundice.
Right: expression with respect to in-vitro test method.

though present, makes itself known to us only under very special conditions of the environment. In this instance the disease for which it may be responsible is not obviously familial and its effects are detectable in healthy persons only by laboratory means. Contrast the two pedigrees of the same family in Figure 1.

People who manifest hemolysis and jaundice after eating fava beans appear to have the same red cell defect, and one sometimes obtains a history of relatives who have had a similar disease[17]. Here the cultural habits of the family determine the familial nature of the disease in contrast to that caused by drugs. The gene is found in high frequency in populations of Mediterranean origin, and it is a geographical accident that the fava bean grows most readily in the same area[18]. Had the plant been indigenous instead to northern Europe, favism might be no more a familial disease than is naphthalene poisoning. One wonders how many other such genetic susceptibilities there may be in which a similar special and relatively uncommon environmental condition must obtain for the characteristic to become readily apparent.

The point of this essay may be simply stated. Gene effects, like gold, are where you find them. They may be obvious or they may be obscure. There are many ways to describe them, many levels at which to study them. They are infinitely modifiable, and indeed in each individual, in greater or lesser degree, must be unique; but they are all traceable to

that relationship of specificity between the genetic material and those molecules which exert qualitative and quantitative control over the metabolism of the living cell. We are really only beginning to understand the influences of the genes on human variability. The genetic method can isolate and circumscribe the problems to be studied with a high degree of refinement, but it remains for the biochemist to elucidate them.

REFERENCES

1. Benzer, S. The elementary units of heredity, p. 70 in: *A symposium on the chemical basis of heredity.* Baltimore, Johns Hopkins Press, 1957.
2. McElroy, W. D. and Glass, B., editors. *A symposium on the chemical basis of heredity.* Baltimore, Johns Hopkins Press, 1957.
3. Gaebler, O. H., editor. *Enzymes: units of biological structure and function. An international symposium.* New York, Academic Press, Inc., 1956.
4. Wagner, R. P. and Mitchell, H. K. *Genetics and metabolism.* New York, Wiley, 1955.
5. Hunt, J. and Ingram, V. M. Allelomorphism and the chemical differences of the human hemoglobins A, S and C., *Nature 181:*1062-63, 1958.
6. Beutler, E., Dern, R. J., Flanagan, C. L. and Alving, A. S. The hemolytic effect of primaquine. VII. Biochemical studies of drug-sensitive erythrocytes, *J. lab. and clin. Med. 45:*286-95, Feb., 1955.
7. Beutler, E., Robson, M. J. and Buttenweiser, E. The glutathione instability of drug-sensitive red cells, *J. lab. and clin. Med. 49:*84-95, 1957.
8. Carson, P. E., Flanagan, C. L., Ickes, C. E. and Alving, A. S. Enzymatic deficiency in primaquine-sensitive erythrocytes, *Science 124:*484, 1956.
9. Sidbury, J. B., Jr. The biochemical pathogenesis of galactosemia, *A. M. A. J. Dis. Child. 94:*524, 1957.
10. Childs, B., Sidbury, J. B., Jr. and Migeon, C. J. Glucuronic acid conjugation by patients with familial nonhemolytic jaundice and their relations, *Pediatrics,* in press.
11. Axelrod, J., Schmid, R. and Hammaker, L. A biochemical lesion in congenital, non-obstructive, non-hemolytic jaundice, *Nature 180:*1426-27, 1957.
12. Hsia, D. Y-Y. The laboratory detection of heterozygotes, *Amer. J. hum. Genet. 9:*98-116, 1957.
13. Holzel, A. and Komrower, G. M. A study of the genetics of galactosemia, *Arch. Dis. Childh. 30:*155-59, 1955.
14. Anderson, E. P., Kalckar, H. M., Kurahashi, K. and Isselbacher, K. J. A specific enzymatic assay for the diagnosis of congenital galactosemia, *J. lab. and clin. Med. 50:*469-77, 1957.
15. Kirkman, H. N. and Bynum, E. Enzymatic evidence of a galactosemic trait in parents of galactosemic children, *Ann. human Genetics,* in press.
16. Zinkham, W. H. and Childs, B. A defect of glutathione metabolism in erythrocytes from patients with a naphthalene-induced hemolytic anemia, *Pediatrics 22:*461-71, 1958.
17. Zinkham, W. H., Lenhard, R. E. and Childs, B. A deficiency of glucose-6-phosphate dehydrogenase activity in erythrocytes from patients with favism, *Bull. Johns Hopkins Hosp. 102:*169-175, 1958.
18. Szeinberg, A. and Sheba, C. Hemolytic trait in Oriental Jews connected with an hereditary enzymatic abnormality of erythrocytes, *Israel Medical Journal 17:*158-68, 1958.

PRESERVATION OF RENAL FUNCTION IN THE PARAPLEGIC*

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Following World War I, it was possible, for the first time, to study a number of patients who survived the initial shock of spinal cord injury. These studies were, of necessity, of only the very early complications, as it was noted by the British and American Medical Corps that 90 per cent succumbed within the first year. Only 20 per cent of the American paraplegics could be evacuated. The great majority of the deaths were reported to be caused by urinary tract sepsis.

The medical literature between the World Wars is for the most part devoid of any study which considers the late urinary tract complications. Only an insignificant number survived for longer than three years during this period, making it impossible for any one individual or group to observe a sufficient number of long term injuries to form definite conclusions as to the treatment of the late complications.

With the employment of the broad spectrum antibiotics in the mid and late 1940's the early complications of severe infection and calculosis, which caused the majority of deaths, have for the most part been eliminated. There has been a complete reversal of the mortality rates of those following World War I, allowing us and others to observe several thousand paraplegics over a period of ten or more years.

Mortality

Despite the over-all improvement in the management of these patients, late urinary tract complications of chronic infection, amyloidosis, hydronephrosis, calculosis, and vesicoureteral reflux causing renal insufficiency, remain the number one cause of death.

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TABLE I.—MORTALITY STATISTICS IN THE PARAPLEGIC

Reporting	*No. Cases*	*Over-all Mort. per cent*	*Urinary Tract per cent*
Barber and Gross—(1952)	506	7.1	57.8
Guttmann—(1954)	1,000	8.3	—
V.A. Hosp., Long Beach, Calif.	1,253	9.0	31.5
McGuire V.A. Hosp., Richmond, Va.	1,000	8.7 {55 Aut. {32 No	24.2 {20.3 {33.2
Stone—(1950)	272	2.9	50
Talbot and Lyons—(1950)	182	7.2	45
Damanski and Gibbon—(1956)	116	23.0	64
Lord and Bunts—(1956)	134	15.0	38

The over-all mortality rate (Table I), as reported by those reporting on 500 plus paraplegics, has been from 7.1 per cent of 506 reported by Barber and Gross, to 9.0 per cent of 1,253 patients reported by the V.A. Hospital, Long Beach, California. Urinary tract complications as the cause of death vary from 24.2 per cent (McGuire V.A. Hospital) to 57.8 per cent (Barber and Gross).

The average longevity after onset of paraplegia, as noted in the 55 patients on whom autopsy was performed at our hospital, was 43.6 months; the non-traumatic paraplegic lived an average of 31.6 months, whereas the traumatic paraplegic survived an average of 52.8 months. Pyelonephritis was listed as an anatomical diagnosis in 33, or 64.7 per cent.

In those reporting smaller series, the death rate from urinary tract complications has varied from 38 per cent of 134 tabulated by Lord and Bunts, to 61 per cent of 116 patients reported by Damanski and Gibbons.

STUDIES OF RENAL FUNCTION

Infection, dilatation of the upper urinary tract and urolithiasis reach their maximum incidence within the first two years, but loss of renal function becomes more common after the third year.

Comarr, in screening the renal function by excretory urography in 315 paraplegics, found that 12 per cent had grade I (no contrast media in 5 minute plate), 8 per cent grade II (no contrast media in 5 and 15 minute plates), and 6 per cent grade III changes (no contrast media

TABLE II.—RENAL FUNCTION STUDIES IN THE PARAPLEGIC

Reporting	*Type of Study*	*No. of Patients*	*Over-all per cent Impairment of Renal Function*
Comarr (1954)	Excretory Urography	315	26 {Grade I—12 Grade II— 8 Grade III— 6
Rogers and Bors (1950)	Conc. & Dilu. PSP	70	52.85 impaired C&D 77.14 impaired PSP
Morales, Sullivan & Hotchkiss (1956)	Inulin and PAH Clearance	62	45.2 Inulin filtration {Gr. II—22.6 Gr. III—16.1 Gr. IV— 6.5 54.9 Effective Renal Plasma Flow {Gr. II—37.2 Gr. III—14.5 Gr. IV— 3.3
Hutch and Bunts (1951) Lord and Bunts (1956)	Excretory Urography	170	22
McGuire VA Hospital (1957-58)	Inulin and PAH Clearance	15	6.7 (Morales et al.)

in any plate), (Table II). His findings closely approximate ours, of an over-all 22 per cent incidence of impaired function in 170 patients. Rogers and Bors, using phenolsulfonphthalein excretion as an indication of tubular excretion, and the concentration and dilution test as a determination of tubular re-absorption, found that 77.14 per cent and 52.85 per cent respectively showed impairment of renal function. Morales, Sullivan and Hotchkiss, in performing the very sensitive tests of inulin and para-aminohippurate clearance on 62 patients, found that almost 50 per cent of their patients revealed loss of renal function.

Paraplegia in itself is probably not conducive to impairment of renal function. Recently, we have performed inulin and PAH clearance studies on 15 paraplegics. Fourteen had been injured less than one year (41–338 days). One World War II injury with a history of prolonged bilateral vesicoureteral reflux was studied.

All patients had received testosterone as an anabolic agent. Thirteen had received Mandelamine chemoprophylaxis from 1-12 weeks prior to the study. None had calculi and none were completely immobilized

at the time of the study. In 14, the inulin and PAH clearances were normal when corrected to body surface area. The World War II injury with severe prolonged reflux had severe impairment of both functions.

Factors Causing Impairment of Renal Function

In an analysis of our patients and other series, we find that all agree that the extent of the traumatic lesion is not of consequence, and, also, that there is a higher percentage of renal disorders in the patient in whom the paraplegia is due to tumor or disease. Some are of the opinion that the cervical and high thoracic injuries have less impairment of renal function, but we feel that the traumatic lower motor neuron injury results in less upper urinary tract damage. First, it is very rare to have an injury so severe as to produce an autonomous bladder. Second, spasm is very rare. Third, the abdominal muscles are preserved. And fourth, there is a greater awareness of a full bladder which is an aid in bladder training.

Most important is the duration of the illness, and allied closely with duration is the status of bladder function. Morales and associates noted that 58-59 per cent had good renal function from 1-5 years but only 27-36 per cent showed good renal function after five years.

In following a group of 170 patients for a period of 10 years, we have observed that it is not the duration of the paraplegia *per se* that results in deterioration of renal function but it appears to be related more directly to the type of bladder function which has been present over a period of years and to whether catheter drainage has been present at all times. We have previously classified a good neurogenic bladder as a bladder that has a sufficient capacity in order that it will not empty more often than every two hours and then with a residual of less than 100 milliliters.

We have noted that there has been a moderate deterioration in renal function over a ten-year period in the entire group. When the function is tabulated as to the status of the bladder function, it is apparent that those patients who have good bladder function without catheter drainage show improvement of function over the ten-year period. Conversely, the patients who must depend on catheter drainage, with the ever-present infection that invariably accompanies such drainage, show a progressive and alarming rate of renal impairment.

From our findings and those of others, it appears that, in order to preserve the function of the upper urinary tract in the paraplegic, it is first necessary to obtain a so-called good neurogenic bladder. In 1949 the statement was made by Talbot and Bunts, "As the bladder goes, so go the kidneys." We have been accused of being dogmatic in this view, but from our studies over the past 12 years, we have found little to cause a substantial alteration of our opinion.

The complications, most often resulting in the development of a poor neurogenic bladder are: 1) An imbalance between the expulsive forces of the detrusor muscle and the obstructive forces of the sphincteric mechanism; 2) spasm due to erratic impulses arising from the isolated sacral reflex centers giving rise to a trabeculated hypertonic and often contracted bladder; 3) infection.

Hypertrophy or spasm of the bladder neck, causing inability to empty the bladder, is present in about 20 per cent of paraplegics. We have found it necessary to carry out 239 transurethral resections on 188 patients. Our results have been excellent in 60 per cent and fair to good in another 20 per cent. The best results were obtained in those patients with an autonomous or lower motor neuron type of bladder.

Nerve interruptions, such as *Pudental Neurectomy*, in the patient who has spasm of the external sphincter, have been useful in a small number of patients. Bilateral *Anterior-Posterior Rhizotomy* which involves the interruption of the nerve segments from D 12 through S 5 will produce a hypotonic type of bladder which may be partially emptied by Credé or other external means. Although there is no neurophysiological explanation, it has been noted by Mierowsky, Shibert and Hinchey and by Brendler and associates, that interruption of only one side of the reflex arc is not always successful. *Subarachnoid alcohol injection* which produces a chemical neurectomy, although successful in the majority, has been found by us and others to be temporary and incomplete in many patients with little or no effect on the tonicity of the bladder.

It is the opinion of most workers in the paraplegic field that the aforementioned two procedures should be used only for the control of skeletal muscle spasm and are only occasionally indicated in the establishment of satisfactory bladder function. *Selective sacral rhizotomy* in the individual with a so-called "inhibited reflex bladder" has produced excellent functioning bladders in four patients in our series.

In many patients it has been found that one procedure alone may not be successful and it may be necessary to use a combination of nerve interruption with transurethral weakening of the internal sphincteric mechanism.

In our opinion, nerve interruption may have its greatest usefulness in the management of upper urinary tract complications and will be considered later.

Prophylactic and Definitive Treatment Measures for Preservation of Renal Tissue

Infection has been and still remains the number one urinary tract complication that may not only cause death, due primarily to an acute fulminating pyelonephritis, but is the primary etiologic factor in the production of many urinary tract complications in the paraplegics, viz., stones, reflux and hydronephrosis.

Infection of the bladder is said to occur spontaneously within 72 hours following cord injury. Therefore, it is thought by most that catheter drainage should be instituted almost immediately. Over-distention of the bladder with myogenic changes probably delays reflex contraction of the detrusor muscle. The above statements remain to be proven, as a large number of patients have not been treated without catheter drainage since World War I. With our present excellent means of combating infection, it might be possible to manage some of these patients without using catheter drainage. From the time of the first introduction of the urethral catheter or suprapubic tube for drainage, infection is present and remains so until tube drainage is no longer necessary.

The area below the level of the umbilicus in the paraplegic is highly contaminated with all organisms found in the lower bowel and those present in decubiti. Catheter urethritis being always present, each reintroduction of a catheter leads to further inoculation of the bladder. It has been noted by Kenny and associates that organisms will ascend drainage tubing unless there is a positive hydrostatic pressure outflow of fluid. This is seldom present and unless a non-corrosive antiseptic solution is present in the drainage collector, infection will result.

As tube drainage is felt to be necessary during the period of spinal shock, what measures may be employed to minimize infection? Suprapubic drainage has been used in the past by many but at present, in

the Veterans Administration Hospitals, is used only for diversion in the treatment of lower urinary tract complications and occasionally for drainage in the quadraplegic and female paraplegic. Hutch and Bunts, in 1951, found that a smaller number developed good neurogenic bladders when drainage was completely or predominantly by suprapubic means.

Our percentage of patients who developed urethral and genital complications has been greatly reduced by the use of small 14 F 5ml. Foley catheters which are taped back to the abdomen, thus reducing the acute angulation at the peno-scrotal junction.

Ross, Gibbon and Damanski of Liverpool, for the past year, have used a polyethylene or polyvinyl catheter in which the inside diameter of the No. 8 F plastic catheter is larger than the inside of a No. 18 F Foley catheter. This catheter may be left indwelling without change or irrigation for 6 or more weeks. Urethral fistulae and pressure sores have been practically eliminated in their patients. We have recently used these catheters and have found them to be most useful during the period of bladder hypofunction.

Blockson has recently described drainage of the bladder by an external bladder pouch in a patient with impassable urethral strictures. We believe that this means of drainage might be applicable during the period of spinal shock with excision of the external pouch and closure of the bladder when reflex contractions have been re-established. Also, it may prove useful in those traumatic quadraplegics, especially in the female in whom there is a total incontinence or in whom it is impossible to eliminate urethral catheters. We have used this procedure in one female patient with an extreme hypertonic uninhibited bladder due to multiple sclerosis and have been very gratified with the results. Before the procedure, she would expel a 60 ml. Foley catheter bag and continually soil her bedding. At present, all drainage is into a Rutzen bag and there is no leakage from the urethra.

In the later stages of paraplegia when all methods for the re-establishment of urethral voiding have failed, a few of us are coming, gradually but surely, to the conclusion that we must rid the paraplegic of drainage tubes even though it may be necessary to resort to the production of total incontinence, using external appliances for the collection of urine.

Semans, in 1945, carried out membranous urethrolysis and urethro-

plasty on 17 patients at our hospital. We have observed the majority of these patients over the past 12 years and in all, who now have total incontinence, the upper urinary tract has remained in excellent condition.

Gibbons, during the past year, has divided the external sphincter in 11 patients using the Thompson resectoscope. He states that although bleeding at the time of the procedure may be troublesome, the end results have been satisfactory.

Organisms may reach the kidney in the paraplegic by direct involvement of the ureteral wall, by the blood stream, or periureteric lymphatics. In our opinion, the most likely avenue of involvement is from direct luminal regurgitation. A high percentage of paraplegics have reflux of clinical significance and undoubtedly many more have temporary periods of incompetence of the vesicoureteral valve mechanism.

At the present time, all paraplegics entering our hospital are immediately placed on prophylactic chemotherapeutic agents which are administered continuously during the early periods of paraplegia. Later, drug-free intervals may be possible. Antibiotics are used only in the patient with clinical evidence of urosepsis. Uncomplicated pyelonephritis resulting in renal insufficiency or renal hypertension has been of rare occurrence in over 1,000 paraplegics treated by us.

Renal calculi or ureteral calculi have occurred in 5.7 per cent of 1,000 paraplegics. Forty-two of these were renal. Nine were bilateral. These 1,000 patients were admitted to our hospital on the average of five months following injury. It has been found that if proper management is instituted immediately, the incidence of upper urinary tract stones will be reduced to 1-2 per cent.

Hypercalcemia is present to some degree in most paraplegics. We are of the opinion that this factor is not of primary importance. It has been reported that the patient who is immobilized for long bone fractures over a period of many months, if given adequate fluid intake and if catheter drainage is not required, will seldom develop calculi. Stasis of urine with ever present infection must be combated by forcing of fluids, and early ambulation and passive exercises.

In the patient who develops upper urinary tract stones, surgical removal should be postponed if the stone is not causing obstruction, until the patient becomes ambulatory. The paraplegic should be closely observed and never be allowed to form stag horn calculi. It is manda-

tory that nephrectomy be avoided and renal tissue be preserved.

Hydronephrosis without reflux is observed in a small percentage of paraplegics and is thought to be due to anatomical changes that occur in the bladder at or near the intramural ureter. On studying the patient with this condition, we find that there is an apparent area of constriction which is located in the area of the intramural ureter. We have found that it is possible to pass large catheters or bulbs through this area without encountering obstruction. Usually this area of obstruction has been found in the patient with a spastic and trabeculated bladder. Severe cystitic involvement due to infection or "egg shell" type stones, when eliminated in some patients, results in a disappearance of the obstruction. In the past, Hutch, Brendler and associates, and more recently, we, have shown that the physiologic obstruction in the terminal end of the ureter may often be eliminated by reducing hypertonicity of the bladder. Hutch noted the disappearance of hydronephrosis in four patients, two following sacral neurectomy and two after complete conectomy. Brendler and associates, in performing lumbosacral anterior–posterior rhizotomy in 10 patients and sacral neurectomy in two, noted marked improvement in three of four patients with hydronephrosis. They believe that relaxation in the region of the vesicoureteral junction following rhizotomy may account for the loss of the hydronephrosis and noted that perhaps sacral neurectomy should be done earlier in selected paraplegic patients to promote better drainage from the ureters.

Recently we have eliminated the reflex arc in several patients. In the first, a patient with bilateral hydronephrosis, more severe on the right, the condition was completely eliminated on the left and much improved on the right, 22 days following conectomy. The second had a hydronephrosis on the left which disappeared five days following subarachnoid alcohol injection. The third had a non-functioning left kidney and a beginning hydronephrosis on the right. Five days following alcohol injection the hydronephrosis was eliminated.

Vesicoureteral reflux, in our opinion, is due to the same etiologic processes that cause non-obstructive hydronephrosis. As yet, it has never been determined that the interruption of any one nerve or group of nerves will result in reflux. Cystograms carried out by us in 22 cadavers showed no reflux to be present with overfilling of the bladder with contrast material.

Reflux of clinical significance has been present in 136 of 1,000 paraplegics observed by us. In 31 the reflux was considered to be irreversible. In these patients the bladder was found to be trabeculated and in a majority, a saccule or diverticulum was found in or near the intramural ureter. We believe that the ureter has lost its muscular support beneath, and loss of obliquity permits regurgitation of the vesicle contents.

It is known that the intramural ureter acts only as a conduit having no circular fibers for peristaltic conduction. When sacculation occurs, the intramural ureter becomes extra-vesicle, losing its normal support. The intramural ureter may then act as an obstruction.

Hydronephrosis and hydroureter in the patient with reflux may develop from one of two causes; first, dilation from the regurgitating column of the fluid; and secondly, due to the anatomical and physiological changes in the bladder involving the terminal ureter as described above.

The prevention of the development of reflux is probably not possible at present but may be lessened in severity and somewhat in incidence by elimination of infection, stones, and other foreign bodies such as catheters. Some are of the opinion that reflux is of no consequence. This may be true in the patient in whom there is no infection and who is voiding without bladder residual. In the paraplegic with irreversible reflux in whom complete evacuation is never accomplished, some means of correction of reflux becomes necessary.

Nineteen patients, when first seen by us, required nephrostomy drainage to preserve, if possible, the remaining function of these badly damaged organs (Table III). In eight of the patients who required bilateral nephrostomy, seven are now dead. In the patient now living, we were able to carry out vesicoureteral plasty and bladder neck resection. He now has good renal function, voids into an external appliance and has no reflux. Two of the unilateral group have required nephrectomy, five have non-functioning kidneys without nephrostomy, two are still with nephrostomy drainage and in only two has the kidney regained almost normal function. If possible, reflux should never be allowed to progress to the stage where nephrostomy drainage becomes necessary.

We have noted the disappearance of reflux in several patients who had the reflex arc eliminated and are of the opinion that it should be

TABLE III.—NEPHROSTOMY DRAINAGE IN VESICOURETERAL REFLUX

No. Cases	*Laterality*	*Results*
	Bilateral 8	7 Dead
		1 Living and Well — without nephrostomies
19	Unilateral 11	2 Nephrectomies
		5 Nonfunctioning
		2 Have Nephrostomies
		2 Regained Partial Function

eliminated in the patient who has a spastic bladder with beginning reflux that is not considered to be irreversible. We have interrupted the reflex arc in the patient with unilateral reflux to prevent the development of the reflux in the uninvolved ureter and for the prevention of re-occurrence of reflux subsequent to vesicoureteral plasty.

In 31 patients vesicoureteral plasty has been necessary on 51 ureters in which we considered the reflux to be irreversible. Recently we reported in a survey that good results were obtained in 79 per cent of the paraplegic group.

Our indications for operation have previously been reported but may be repeated as being pyelographic evidence of gross damage to the upper urinary tract, repeated attacks of pyelonephritis and irreversible changes as noted by persistence of reflux for more than three months. It should be re-stated that in the presence of irreversible reflux, catheter drainage may never be eliminated unless vesicoureteral plasty is performed.

COMMENT

The paraplegic receives multiple bodily insults which begin with the initial injury and progress through multiple blood transfusions, plastic procedures for decubiti, orthopedic and neurosurgical corrections and innumerable urological procedures for the correction of complications which develop during their care and attempts to establish urethral voiding.

It is mandatory that the paraplegic be considered an arrested, and not a cured patient. He must be followed for the rest of his life. Severe renal damage may occur in the absence of subjective clinical evidence. The patient whose bladder status is excellent upon discharge may have

rapid deterioration of function due to many etiologic factors. Complete urological re-evaluation should be made on all paraplegics at least once every six months.

We must strive by all means at our command to obtain urethral voiding. No patient, paraplegic or otherwise, can long escape the complications that accompany catheter drainage. In a small per cent, drastic measures may be necessary such as the production of total incontinence or the establishment of an external bladder pouch.

There has been remarkable improvement in the management of paraplegics which has resulted in preservation of renal function. We have recently completed a survey on 100 paraplegics who received their injuries between January 1951 and December 1953. We found that although 16 developed reflux, renal function determined by excretory urography showed severe impairment in only two kidneys and mild to moderate insufficiency in seven others. Calculi were observed in two and moderate caliectasis in four kidneys. Of the last 246 patients admitted to our cord injury service, 85 per cent do not require catheters, but the majority require some external apparatus for pseudo-incontinence.

Summary

To preserve and conserve renal parenchyma in the paraplegic, it is necessary to have an ambulatory patient in metabolic balance with satisfactory bladder function, not requiring tube drainage.

Prophylactic, preventive and methods of definitive treatment are discussed.

BIBLIOGRAPHY

Barber, K. E. and Cross, R. B., Jr. The urinary tract as a cause of death in paraplegia, *J. Urol. 67*:494-502, 1952.

Blocksom, B. H., Jr. Bladder pouch for prolonged tubeless cystostomy, *J. Urol. 78*:398-401, 1957.

Bors, E. Neurogenic bladder, *Urol. Surv. 7*:177-250, 1957.

Bors, E. and Comarr, A. E. Vesico-ureteral reflux in paraplegic patients, *J. Urol. 68*:691-98, 1952.

Brendler, H. and others. Spinal root section in treatment of advanced paraplegic bladder, *J. Urol. 70*:223-29, 1953.

Bunts, R. Vesicoureteral reflux in paraplegic patients, *Trans. Amer. Assoc. gen.-urin. Surg. 49*:199-202, 1957.

Bunts, R. Management of urological complications in 1,000 paraplegics, *Trans. Amer. Assoc. gen.-urin. Surg. 49*:184-92, 1957.

Comarr, A. E. Renal changes in paraplegia as screened by routine excretory urography, *J. Urol. 72*:596-605, 1954.

Comarr, A. E. and Bors, E. Further observation on vesicoureteral reflux, *J. Urol. 74*:59-66, 1955.

Comarr, A. E. A long-term survey of the

incidence of renal calculosis in paraplegia, *J. Urol. 74*:447-52, 1955.

Damanski, M. and Gibbon, N. The upper urinary tracts in the paraplegic, a long-term survey, *Brit. J. Urol. 28*:24-36, 1956.

Deitrick, R. B. and Russi, S. An analysis of the autopsy findings in 55 paraplegics: A tabulation and review, *J. Amer. med. Assoc. 166*:41-44, 1958.

Guttmann, L. and others. Discussion on the treatment and prognosis of traumatic paraplegia, *Proc. roy. Soc. Med. 40*: 219-32, 1947.

Guttmann, L. Statistical survey on one thousand paraplegics; and Initial treatment of traumatic paraplegics, *Proc. roy. Soc. Med. 47*:1099-1109, 1954.

Hutch, J. A. Vesico-ureteral reflux in the paraplegic: Cause and correction, *J. Urol. 68*:457-69, 1952.

Hutch, J. A. Non-obstructive dilatation of the upper urinary tract, *J. Urol. 71*: 412-20, 1954.

Hutch, J. A. Treatment of hydronephrosis by sacral rhizotomy in paraplegics, *J. Urol. 77*:123-34, 1957.

Hutch, J. A. and Bunts, R. C. The present urologic status of the war-time paraplegic, *J. Urol. 66*:218-28, 1951.

Kenny M. and others. Retrograde urinary infection along indwelling catheter drainage system in paraplegia, *J. Urol. 75*:737-42, 1956.

Konwaler, B. E. Renal pathology in paraplegia. *Proceedings of Clinical Paraplegia Conference, 2*:42-45, 1953.

Kopp, J. H. Importance of proper urological care in spinal cord injuries, *South med. J. 48*:1044-48, 1955.

Lord, K. H. and Bunts, R. C. Present urologic status of World War II paraplegic: Ten year follow-up, *J. Urol. 75*:66-72, 1956.

Malamant, M. and Bunts, R. C. Transurethral resection and the neurogenic bladder, *Virginia med. Monthly, 76*:243-46, 1949.

Meirowsky, A. M., Scheibert, C. D. and Hinchey, T. R. Studies on the sacral reflex arc in paraplegia; response of the bladder to surgical elimination of sacral nerve impulses by rhizotomy, *J. Neurosurg. 7*:33-38, 1950.

Morales, P. A., Sullivan, J. F. and Hotchkiss, R. S. Renal clearance studies in paraplegics, *J. Urol. 76*:714-22, 1956.

Owen, E. E. and Finch, E. P. Bacteriological study of urine from paraplegic patients, *J. Urol. 61*:258-64, 1949.

Pate, Virgil A., Jr. and Bunts, R. Carl. Urethral diverticula in paraplegics. *J. Urol. 65*:108-25, 1951.

Prather, G. C. Spinal cord injuries: Calculi of the urinary tract, *J. Urol. 57*:1097-1104, 1947.

Prather, G. C. Spinal cord injury: Some urological aspects, *J. Urol. 86*:347-54, 1951.

Riches, E. W. Discussion on the treatment and prognosis of traumatic paraplegia, *Proc. roy. Soc. Med. 40*:225-29, 1947.

Rogers, G. W. and Bors, E. Kidney function in patients with paraplegia, *J. Urol. 63*:100-04, 1950.

Ross, J. C. Management of the bladder in spinal injuries, *Brit. med. J. 1*:616-19, 1951.

Ross, J. C. Treatment of the bladder in paraplegia, *Brit. J. Urol. 28*:14-23, 1956.

Ross, J. C., Gibbon, N. O. K. and Damanski, M. Recent developments in the treatment of the paraplegic bladder, *Lancet 2*:520-24, 1957.

Semans, J. H. Neurogenic disease of the bladder: The surgical management of its complications, *J. Urol. 62*:820-32, 1949.

Simons, I. Sterilization of neurogenic bladder by Mandelamine (methenammine mandelate); studies in bladder function, *J. Urol. 64*:586-600, 1950.

Stone, E. P. Functional evolution of the neurogenic bladder in paraplegic patients, *J. Urol. 63*:373-92, 1950

Talbot, H. S. and Bunts, R. C. Late renal changes in paraplegia; hydronephrosis due to vesico-ureteral reflux, *J. Urol. 61*:870-82, 1949.

Talbot, H. S. and Lyons, M. K. Late renal changes in paraplegia; destructive lesions, *J. Urol. 63*:667-72, 1950.

Tinckler, L. F. Some observations on ureteric activity and their clinical significance, *Proc. roy. Soc. Med. 49*:702-08, 1956.

Vinson, C. E., Hutch, J. A. and Bunts, R. C. Evaluation of vesicoureteral plasty for reflux, *J. Urol. 78*:611-19, 1957.

THE DIAGNOSIS AND MANAGEMENT OF ENDOMETRIOSIS

*Transcription of a Panel Meeting**

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MODERATOR ROGER B. SCOTT: I think the major portion of our comments should be limited to a discussion of external endometriosis, the disease entity characterized by the presence of ectopic endometrium located outside the uterus. Our discussion should be limited to this particular aspect because to all intents and purposes internal endometriosis or adenomyosis, involvement of the myometrium from within, is generally considered to be a different disease entity and possibly has a different pathogenesis. Dr. Javert may take issue with me on this. I hope he will.

I should first like to take a few minutes to discuss the histogenesis because of its particular interest to me. I was trained in the school that adhered to the theory of celomic metaplasia,—that the celomic epithelium could be induced, by irritation or other means, to produce or be altered into endometrial tissue. The original work with TeLinde and Wharton was begun in the belief that the cast-off endometrium was not viable. We believed that the crux of the problem lay in finding out whether or not these fragments of endometrium, shed at the time of menstruation, were viable. We performed several experiments on monkeys to determine this. In some we turned the uterus so as to allow the menstrual discharge to drain directly into the abdominal cavity. In others, the cervical portion of the uterus was transplanted into the rectus muscles of the abdominal wall. The results of these experiments indicated two things that led us to believe that the shed endometrium *was* viable. First, without direct continuity and apparently as the result of direct contact with the shed endometrium we were able to produce endometriosis from this cast-off material. It could be produced not only within the peritoneal cavity but extra-peritoneal as well. The peritoneum was not essential for its production. Secondly, in transplanting endocervical tissue, squamous epithelium of the cervix, and epithelium of the endosalpinx to various areas we found that these tissues maintained the same histologic structure characteristic of their point of origin. They did not change to endometrial tissue.

It was interesting to find, when the six monkeys studied were finally autopsied, that all had developed extensive endometriosis and that all had lymph node involvement. This result required a complete reversal in our approach to this problem. I have now become a little too enthusiastic about the Sampson theory of retrograde menstrual

flow, transplantation and shedding, with the possible addition of lymphatic and vascular spread.

We believe that the work with monkeys is reasonably valid because the monkey is a menstruating primate. The uterotubal junctions of the monkey are open, as they are in the human female, and also the reproductive menstrual physiology is essentially the same as it is in the human female.

Recently, in looking over some material on primate physiology, an additional item was encountered which I found rather interesting. This makes the relationship even more pointed. I quote now from an article which was written in 1871; in comparing the human female with female monkeys, it says:

"As monkeys had the habit of turning their hinder ends towards other monkeys, it ceases to be at all surprising that it should have been this part of their bodies which had been more or less decorated; that is, the sexual skin."

So, shades of the bustle and the tight skirt! Maybe women and monkeys are not too different in some respects!

We have not dealt with another problem already mentioned and that is the possibility of retrograde flow of shed endometrium through the tubes. A sufficient number of studies have demonstrated that the opening is large enough to allow the passage of the tissue and this lends support to the idea of transtubal spread. Relevant observations have been made at operation on those with retrodisplaced uteri. Twelve patients with this condition were operated upon about the second day of the menses and in each instance from 10 to 60 ml. of blood or fluid material was found in the cul-de-sac. In the material from two of these, endometrial glands and stroma were found. As further clinical evidence, I am sure many of you have observed bloody fluid in the cul de sac at laparotomy after a preliminary curettage (without perforation by a sound or curette) has been done. Of course the presence of this material after curettage is not a regular occurrence, but it does occur.

Various explanations have been offered to account for umbilical endometriosis and implants of the same type in other areas, such as the pleura and the extremities. We know of cases in which endometriosis has been found in the upper extremities, in the thigh, etc. It is known that intra-abdominal carcinomas metastasize to the skin and to the

extremities and that prostatic cancer spreads to bone. We don't have too satisfactory an answer as to why they do. We believe that Batson's paravertebral plexus plays a part, particularly in the spread of carcinoma of the prostate to bone.

Some work has recently been reported which indicates that arteriovenous shunts within the lung may explain why this material, once it gets into the lung, does not necessarily implant but may travel right on through the lung to a peripheral area. These shunts apparently permit cell masses as large as 500 micra to cross over without implanting. It has been shown, for example, that, after an injection of mouse tumor cells into a rabbit's ear vein, tumor cells can be picked up from the aorta within one to three minutes. If this material is injected back into the mouse, the same malignancy is produced. These cells must be capable of traversing the pulmonary circuit without necessarily implanting and then shedding. Certainly we have had many experiences with trophoblastic tissue which travels to the lung with considerable ease, invades vascular channels to get there, and also travels to various other areas of the body.

I have here some slides, at least one of which explains my thinking regarding umbilical endometriosis. (Slide) This is an example of umbilical endometriosis, seen about 12 years ago. There was a focus in the pelvis. The patient had previous surgery for endometriosis of the ovary.

(Slide) This shows an interesting instance of a patient who sustained a tear in the lateral uterine wall at a term delivery. A large hematoma, which measured about 6 cm., developed in the broad ligament; this did not increase in size and it was observed over a period of time. After about four days the patient developed a Cullen's sign of the umbilicus. This results from a deposition of blood pigment in and about the umbilicus, pigment which has apparently been transported from the pelvis. Umbilical endometriosis can be explained in much the same manner. Endometrial tissue may travel to the umbilicus from the pelvis by traversing the lymphatic channels. We have seen pelvic carcinoma metastasize in this fashion.

Dye studies in monkeys and in two humans who had laparotomies have shown that the dye concentrates in channels alongside the obliterated hypogastric arteries. So it may be that these endometrial particles travel lymphatically in a retrograde fashion.

(Slide) This slide shows an endometrial transplant into the abdominal wall of a monkey, done three years ago. Notice the arrow in the area of transplanted endometrium.

(Slide) In that area which is enlarged in the next slide you see what apparently is a mass of endometrial epithelium within a lymphatic or vascular channel. This is just an incidental finding and Dr. Javert will talk more about this condition later.

(Slide) There was one patient who reproduced the same findings observed in our monkey experiments; a woman who had a single uterus from the left Müllerian system and a horn on the right which did not communicate with the left uterus but shed endometrium into the peritoneal cavity. She had very severe pelvic pain when she was 11 to 13 years of age and this continued as dysmenorrhea up to the age of 21. Unfortunately, she had had her left tube and ovary removed with the result that at age 21 her main problem was four days of dysmenorrhea plus infertility. At operation we found extensive endometriosis, large cystic areas, and hemosiderin deposits, involving the whole right side of the pelvis, apparently secondary to shedding of endometrium into the pelvis from this right horn. This horn had no communication with the uterine cavity and hysterography proved this lack of continuity.

(Slide) The behavior is very similar to that of carcinoma. It differs only in that endometriosis is histologically benign. It can spread by direct extension and by implantation after first shedding out the tubes in retrograde fashion. It can spread from a parent or a daughter implant. It can spread by way of the lymphatics and blood vessels and there is probably distant spread by these channels.

Endometrium is a very rapidly growing and extremely active tissue; there is hardly a tissue in the body that has such a potential for growth. The shed fragments can transplant onto the surface of the cervix, onto raw areas in the vagina, and on the vulva.

I have been particularly fond of Dr. Carl Javert's theory of benign metastases and I should like to call on him to give his views on the subject.

DR. CARL JAVERT: The first speaker has stolen most of my thunder. He has already given you a perfect description of the theory of benign metastases. I think I could well sit down without saying anything more, but I am not going to do that because I have a few slides that support

what has already been said. At the outset, may I say that I heartily disagree with anyone who believes in the theory of celomic metaplasia. That theory is of historical interest only.

The previous speaker has referred to the widespread distribution of the extrauterine lesions of endometriosis. He mentioned those in the thigh, the forearm, umbilicus and referred to those in the pleura. He might also have mentioned the appendix and the small and the large bowel, the abdominal incisions, the hernial sacs, inguinal lymph nodes, the groins, the lesions on the vulva, those on the bladder, the cul-de-sac, the cervix, the rectosigmoid, pelvic lymph nodes, tubes, ovaries, endometrial cysts, implants on the pelvic peritoneum and he indicated that such widespread distribution is very analogous to the spread of malignant endometrium. Sampson, in 1925, made a similar comparison between the spread of benign endometrial tissue and malignant endometrial tissue as did Javert in 1952. The Sage of Baltimore, Dr. Emil Novak, has had those in Baltimore confused for many years saying that regurgitated endometrium does not implant. Therefore Dr. Scott had to go into the laboratory and perform his celebrated studies on the monkey, in order to show that regurgitated endometrium did implant. He has shown that Novak was wrong. Yet if one goes into the historical background of this condition one will find that Dr. Novak feuded for many years with Sampson over this concept. Sampson, of Albany, N.Y., has had many enthusiastic supporters not only in New York City but throughout the State. We have always accepted Sampson's theory and believe that Dr. Scott's experimental work has definitely confirmed this explanation of the etiology of endometriosis.

Many years ago, Goodall of Montreal emphasized that in order to have this disease the patient had to have a uterus. In addition to a uterus it is necessary to have a functioning endometrium and that implies the presence of functioning ovarian tissue. With these two tissues present, the stage is set for spread and dissemination by many avenues. Those avenues include the lymphatics, as Halban postulated in 1924, and the vascular channels, as Sampson postulated. Other lesions have been produced by implantation and they have followed direct extension, as Dr. Scott indicated.

Cullen and others showed adenomyosis to be evidence of direct extension. Today we call this direct invasion of the myometrium. This

tissue exhibits an ability to extend in this particular fashion just as does endometrial cancer.

When we study cases of adenomyosis, we prepare lateral cornual sections of the uteri. One can often find extension of the process in the bases of the broad ligaments on either side. That explains the thickening and induration that we feel so often on pelvic examination of these women who have rather widespread endometriosis.

On further sectioning of the cornual angle of the tubes including the isthmus, one can often find isolated channels looking like lymphatics and perhaps blood vessels in which endometrium is spreading laterally to either side of the uterus. Are these artefacts, as suggested by the earlier pathologists? When one sees several of these "artefacts" in the same low-power field one can only wonder whether they are truly artefacts or whether they are not the real lesion.

With higher magnification many sections of the myometrium will show endothelial-lined structures containing bits of endometrium within them, often attached to the walls of the lumen of the particular channels. So, if we have lesions distant from the uterus we must find the intercommunicating channels of spread. Consequently, there is something to the theory of benign metastases.

There are other instances of such benign metastases, for example, the trophoblastic tissue which invades the uterus and is transported to the lung. Another example is the benign metastasis of certain thyroid lesions. We also see pseudomyxoma peritonei as evidence of benign spread when pseudomucinous cysts rupture. Certain papillovarian tumors metastasize to the peritoneum. The so-called endosalpingioma has a habit of developing multiple transplants on multiple surfaces.

The endometrium can spread to the uterotubal junction as in one of our cases. On several occasions we have seen this lesion associated with ectopic pregnancy. A little further along the tube one may find menstruating endometrium as in another specimen. This poses the question of lesions of endometriosis providing cells which in turn implant and metastasize according to Sampson's concept. They do not always need to be regurgitated from the menstruating uterus. Secondary implants may in turn disseminate cells which in turn become, if you will, tertiary implants.

Every now and then, following curettage and hysterectomy, one may find in routine sections of the tube, in the endosalpinx, isolated

fragments of endometrial tissue on their reverse way along the tube, perhaps as a result of the curettage. On occasion, at laparotomy after curettage, one finds blood in the cul-de-sac, as Dr. Scott has mentioned. On another occasion we have found a blood clot in the fimbriated end of the tube. Being curious, we sectioned this clot and found it to contain definite and quite visible-looking endometrial tissue.

Endometrial fragments can implant and do deposit themselves on serosal surfaces and do continue to grow there because of hormonal influences. I do not think we need to invoke the theory of celomic metaplasia to explain their presence. This theory was proposed by Ivanoff, who wrote in Russian. I have not read this in the original and I would doubt that anyone in this audience has either. Yet we keep repeating this unproven theory as a fact. In similar fashion we perpetuate ill-founded beliefs based on hearsay evidence, without having read the original report or even a translation of it.

The next few illustrations are from Sampson's celebrated article published in 1921, and they show implants on the ovary, the appendix, and powder burns on the round ligaments and broad ligament areas.

(Slide) Here is an endometrial cyst of the ovary and a fairly good one, full of chocolate colored material, hemosiderin pigment with characteristic epithelial lining and glands in the stroma. The next slide shows a bowel obstruction, which I am sure all of you have seen from time to time.

This section of ovary has a large island of endometriosis deep in the hilum of the ovary, far away from any surface celomic relationship.

Let us now consider the lymphatic system. In the early days we were interested in removing a few pelvic nodes to see if the tissue did disseminate to those structures. As luck would have it, the very first periureteral node removed and studied had endometriosis. Note the two areas of endometriosis, one in the peripheral sinus of the lymph node; the other is deeper, and contains stroma and glands. The glands and stroma are definite under higher power. Note the secretion in the gland, the pseudostratified epithelium, the stromal reaction surrounding it, all contained in the lymph node.

Occasionally these lesions occur in the cul de sac posteriorly as adenomyomas. They may surround the ureters and spread to the vaginal vault. Many of the endometrial lesions of cancer metastasize to the same site in the vaginal wall as does this benign endometrial tissue.

Now let us consider Victor Marshall's celebrated case of endometriosis in the kidney. Note the glomeruli in one half of this low-power field, and the endometrial stroma and glands in this other portion of the kidney lesion. Several other cases have been reported, one by Maslow and Learner. The presence of endometrial tissue in Marshall's case in the kidney has been confirmed by many pathologists.

(Slide) Recently Lattes has reported a lesion in the lung. Here we see the alveoli, some of them collapsed and full of blood and pigment and debris and here a nodule with endometrial glands in it and a decidual reaction in the stroma. This patient was four months pregnant. The lesion in the lung had been present for some time, but it became larger during pregnancy. Howard Taylor had seen the case and diagnosed endometriosis of the lung clinically. Then the patient became pregnant and the lesion increased in size. A biopsy showed this gland and marked decidual reaction in the stromal cells surrounding the glandular elements.

To summarize, we have presented the theory of benign metastasis which incorporates Sampson's concept of implants and Halban's concept of lymphatic spread, as well as other concepts of direct extension, vascular spread, spread to the lymph nodes, and distant hematogenous spread to the kidney and to the lung. Arteriovenous shunts in the lung as reported by Lachman, and bearing in mind Batson's paravertebral circulation, make the theory quite tenable.

As Dr. Scott implied, this spread is similar to that of endometrial cancer. Perhaps we should classify endometriosis as we do endometrial cancer and assign cases to various stages:

Stage O—Limited to the endometrium.

Stage I—Adenomyosis uteri.

Stage II—Direct spread to adjacent organs, to the bladder or the ovary, the endometrial cysts, pelvic peritoneum.

Stage III—Lymph node spread.

Stage IV—Distant lesions in the kidney and the lung, thigh or arm, etc.

MODERATOR SCOTT: Thank you, Dr. Javert.

I know that you are as convinced as I am. There are still some contrary opinions in some areas of the country other than Baltimore. So I am going to solicit your help in trying to influence those who still cling to the celomic metaplasia theory!

On one occasion, during one of these heated arguments between Novak and Sampson, closing remarks attributed to Sampson are interesting. Sampson had just about as much as he could take and he closed his remarks in this fashion: in effect he said, let us suppose that there is a forest composed entirely of pine trees except for one oak tree and underneath this oak tree there are many thousands of acorns. Now it would seem rather ridiculous to presume that squirrels had carried these acorns from another oak tree and put them under this tree.

I have a few questions which I will save for Dr. Javert because I want to ask him how he explains certain things that have bothered me a bit. But we will now go on to the problem of infertility and endometriosis. We know that infertility is high in association with endometriosis. We also know that the tubes are, for the most part, open. I have asked Dr. Buxton to tell us something about the problem of infertility and endometriosis.

DR. CHARLES LEE BUXTON: Dr. Scott, in his introduction, mentioned a few of the most important aspects of infertility and endometriosis and stole some of my thunder too.

There actually isn't too much to say about this subject which is new and different, so I will spend just a few minutes reviewing what is known and possibly refreshing your memory with some of the facts probably known to you in the past.

Of course, as Dr. Scott has said, endometriosis has always been considered an etiological factor in infertility and almost everybody who has written on this subject, Sampson, Kimbrough, Novak, Counseller, Scott and others have mentioned this factor over the past many years. But I don't think anybody has yet figured out just why it is that this is so and which actually comes first or which causes which! You might ask not whether the chicken or the egg comes first but whether it is the endometriosis or the egg.

As you all know, back in 1938, Dr. Meigs of Boston somewhat startled the gynecological world by stating that there was a sort of predilection for endometriosis in private patients as compared to ward patients and to substantiate his idea he collected 400 case histories of his private gynecological patients and compared them with 400 ward patients who had been operated upon at the Massachusetts General Hospital. He found that of his private patients 28 per cent had endome-

triosis but that only 5.8 per cent of the ward patients who had been operated upon had it. Later on, to further substantiate this claim he collected another series, with somewhat similar results. He therefore concluded that postponement of pregnancy either produced endometriosis or if a woman did not begin having pregnancies in her early twenties or thereabouts, that endometriosis was likely to develop instead. These certainly are interesting figures but they have not actually been substantiated by anyone else. It may be that Boston women are different. Boston seems to be different in many respects and this may be one of them! But it seems to be more likely that the women in this series of ward cases may have been operated on for so many other things, especially pelvic inflammatory disease, that the incidence of endometriosis has been considerably diluted.

Also, as I am sure most of you know, Dr. Cavanagh, at the Sloane Hospital, made an extensive study of the cases of endometriosis in that Hospital and published his results in 1951. He found no significant difference in the incidence of endometriosis in different economic groups. He did find, however, that endometriosis was definitely associated with infertility in about twice the normal expected frequency in women that were under 30 and about nine times the expected frequency after that age. In other words, women over 30 very frequently had an association of endometriosis and infertility. So it might be said that endometriosis has something to do with infertility and since endometriosis is so much more frequent after the age of 30, there is just that much more frequency with which it is involved in infertility. Since infertility is more frequently due to other causes after the age of 30, there may be a sort of adventitious, non-significant, incidental association. But certainly it must be a constantly increasing etiological factor in infertility.

Of course the crucial question is, why is this so? Does endometriosis actually produce anatomical obstruction in the tubes? I think the answer is, in spite of the evidence in Dr. Javert's slides tonight, probably not.

In order to start a little argument, I should be very interested in seeing some other sections of that tubal epithelium that Dr. Javert showed in some of the slides, because it seems to me that sometimes it is extremely difficult actually to identify endometriosis in a situation like that. Although I am sure it does occur, I believe it is very rare for endometriosis to occur within the tubal epithelium itself. We all

know, of course, of any number of instances where tubal epithelium develops, where endometriosis develops on the serosal surface of the tube and may possibly, as time goes on, invade the muscularis and the tubal epithelium. But, in general, it seems to me that if this does occur, the endometriosis is very likely to develop first on the serosal surface of the tube. Therefore it is more likely to be identified before it has developed to such a degree that the tube is obstructed. Its importance in infertility, therefore, is not necessarily so often one of tubal obstruction as it is something else. Of course, serosal involvement of other structures may naturally incorporate the fimbriated extremity in the endometrial process and therefore possibly close the fimbriated extremity and thereby close the tube. What endometriosis probably does—and this I think is quite important clinically—is to interfere with tubal and ovarian function more than it does with tubal morphology. I believe we are all becoming increasingly aware that this rather largely unexplored area between the fimbriated extremity and the ovary in infertility problems may be one of considerable importance. It may be that many a slip in ovum transfer between the ovary and the fimbriated extremity of the tube occurs and this must be so especially when there is any pelvic pathology present.

When we do salpingograms, for instance, we are, of course, interested in tubal patency but we are also extremely interested in developing techniques to determine whether there is any pelvic peritoneal pathology present which may affect the process of ovum transfer, or the normal physiology of the fimbriated extremity of the tube, or the normal physiology of ovulation in the ovary. It is possible here that endometriosis plays such an important part in infertility, and it seems to me that this should be kept constantly in mind when one approaches the surgical treatment of endometriosis in an individual in whom one wishes to retain or establish fertility potential. In other words, it is extremely important to try to re-establish function as well as the morphology of the tube and the ovary, or whatever happens to be in between. As far as the surgical therapy of infertility and endometriosis is concerned, this is probably as important an aspect as anything else with which we are involved.

MODERATOR SCOTT: I agree that a defect in the transport system seems to be a logical explanation for increased infertility. It is not difficult to accept the idea that a large ovary and an endometrial cyst

can agglutinate to peritoneal surfaces. Should that occur, there may be only a tenth of the surface area of that ovary available from which the tube can pick up an ovum. If the egg should be produced at any other part of the ovary, it would not have access to the fimbriated end of the tube. I believe a mechanical explanation is tenable.

One question that is continually being raised is whether there is something basic and fundamental in the disease process that makes infertility and the disease process more common. I don't know the answer.

Dr. Hellman has just been calling me to account for giving him the subject of the rationale and indications for hormone treatment in endometriosis. I am sure he will have some very appropriate remarks to make about it.

Dr. Hellman!

DR. LOUIS M. HELLMAN: Apparently with the help of a monkey, my old friend, Dr. Scott, has succeeded in making the jump from Ivanoff to Sampson! I would hope that this was the reflection of scientific observation and not of the political climate in which we live!

I can remember very well, as a medical student, being present at a meeting at which Dr. Willard Allen talked about the clinical application of hormones. He talked in particular about estrogen and progesterone and he said that in his experience progesterone had no therapeutic use whatsoever and estrogen had but one, namely, the treatment of menopausal symptoms. He did not mention testosterone but I suspect he would have put it in a similar category also.

Dr. Jeffcoate, of Liverpool, writing in 1934 on endometriosis, in a very exhaustive article, put forward the hypothesis that endometriosis was due to hyperfunction of the ovary. As many of you, who know Jeffcoate and the quality of his mind, are aware, he is an astute and stimulating thinker with a very facile tongue. As one reads this article, one has great difficulty in actually pinning down the points on which this hypothesis is based, but as far as I can gather they are three:

1. That in endometriosis the ovary is frequently the site of multiple follicular cysts.

2. That endometrial hyperplasia and endometriosis are frequently associated.

3. In endometriosis, the glands are hyperplastic and are rarely if ever secretory.

As far as I can discover there is little basis for any of these conclusions in the work that has been done since then.

This work lay all but forgotten until 1940, when Wilson, of the Harlem Hospital here in New York, had a young patient who refused operation of any kind for what was apparently an extensive case of endometriosis. He was at a loss as to how to treat her but conceived the notion that if testosterone were given in large enough doses she could be temporarily sterilized and the symptoms and perhaps some of the lesions would be alleviated. He administered testosterone in what we now would consider a large dose. He gave 4800 mg. over a period of six or seven months. This patient developed hair and acne and unfortunately acquired permanent deepening of her voice. But the interesting thing in Wilson's paper is the statement that the pain and the dysmenorrhea, as a matter of fact menstruation itself, disappeared. Not only did the menstruation and accompanying dysmenorrhea cease but the pelvic pain disappeared and the dyspareunia, of which she complained, also disappeared. I think the last statement of Wilson in this article is one which has been overlooked, that he is not advocating therapy, but that this can be considered as a clinically successful experiment.

This paper was followed shortly by others, particularly by Hirst of Philadelphia, on the treatment of endometriosis with the male hormone. Most observers found, as Wilson had, that the pain and the dysmenorrhea regressed. If the dosage were kept at a proper level the undesirable side effects of the male hormone were not evident and there were claims that the lesions became smaller. All observers stated that the *disappearance* of the clinical lesions which could be palpated vaginally before treatment was questionable but certainly they became smaller in some cases.

Perhaps the best paper, or at least the largest series, was published in 1933 by Preston of Montana. Here 187 cases were treated with male sex hormone, the dosage, by and large, being kept to less than 300 mg. per 30 day cycle. In these patients dyspareunia was relieved in about 80 per cent of the cases and dysmenorrhea also disappeared in about the same proportion. One of the most interesting statements made was that of the 187 patients whom he treated there were 80 who complained of sterility and who apparently had never been pregnant. Of

these, 60 per cent had offspring from one to four years after the treatment. His bad effects were minimal,—hirsutism in 3 per cent and acne in but 1 per cent.

I think all the investigators of this method of treatment are of the opinion that one can relieve the pain, the dysmenorrhea and the dyspareunia with male sex hormone. The great problem of course has been as to how the diagnosis of endometriosis has been made. I suppose that one could criticize all of these papers on this basis, where the diagnosis was made largely on the history of increasing dysmenorrhea and onset of dyspareunia and the finding of thickening in the cul-de-sac and along the course of the uterosacral ligaments.

I believe all of us realize that, although the story is straightforward in many cases of endometriosis, there are many individuals with severe endometriosis who don't have a typical history. Surgeons have been misled many times by a characteristic history but found no sign of this lesion when they opened the abdomen.

Preston and Campbell went back to the Jeffcoate article for their rationale and said that endometriosis was associated with hyperfunction of the ovary and therefore testosterone should be given. The story is a little different with stilbestrol. Goodall in his book, which has already been referred to, states that endometriosis is associated with endocrine imbalance. I suspect that the statement of Goodall was based on the findings of Jeffcoate.

After reading what Goodall had to say, Karnaky, in his article, astutely asks: "If endometriosis is due to endocrine imbalance and hyperfunction of the ovary, then what would happen if massive doses of stilbestrol were given to patients?" So he proceeded to treat 17 patients in this way. The method of giving the drug is, I think, in itself quite exciting. He begins with .3 mg. and this is increased daily to about .5, 1, 2, 3, 4, until he gets to 5 mg. Then 5 mg. is continued until the patient begins to bleed, at which time 10 mg. is given every 15 minutes until the bleeding is stopped and then 10 mg. is continued nightly until the patient starts to bleed, at which time 15 mg. is given every 15 minutes and this keeps on until one gets to 125 mg. of stilbestrol. All of Karnaky's patients were relieved of their symptoms. Many of the lesions became smaller. There was one patient with endometriosis in an abdominal scar and after treatment with stilbestrol

by this method the endometriosis in the abdominal scar shrank to a small white lump. Dr. Karnaky has been referred to facetiously as the "Stilbestrol Kid", and I think many people took this article with a grain of salt. But there were individuals who were enough intrigued with the idea that ovary and pituitary and possible ovarian function could be depressed with large doses of the hormone, to warrant their trying it. Among them was Hertzel who published a report in *The New England Journal of Medicine*, and there were other odds and ends of cases which appeared in various other journals. I think the original contention of Dr. Karnaky that the pain of dyspareunia might well disappear was correct. Certainly, in a large majority of cases menstruation ceased and with it the pain of dysmenorrhea. The claim that the lesions were smaller and more freely movable has not been substantiated.

There is little enthusiasm for the large doses of stilbestrol. As a matter of fact, the side effects of nausea and vomiting which were prominent in the series treated according to the method I outlined, were so severe that these patients had to be treated with rectal administration of barbiturates.

As Dr. Novak, who has been under fire here tonight, said, he could not see why a little barbiturate and codeine might not solve the problem without the stilbestrol.

What sort of patients can be treated with hormones?

Obviously Wilson's first case in which testosterone was used represented a fair example. He described a patient in severe pain, who for some reason or other refused any treatment, either operative or radiation. In this instance I would think that either testosterone or stilbestrol might be used on a temporary basis.

I am unable, from any personal experience, to discuss the question of whether infertility is improved with such hormonal treatments. I think the reports in the literature, particularly those concerning testosterone, are of interest.

Some attempt has been made to use these two hormones as aids in diagnosis. However, when the argument is followed to a logical conclusion, it seems unduly complicated to me and it would appear that other simpler methods can be used to arrive at a diagnosis; to mention one, the culdoscope. One challenging aspect of hormonal

therapy is to determine whether the administration of testosterone or stilbestrol can, by diminishing the edema and the tissue reaction around it, so improve the lesions that the performance of a conservative operation might be facilitated. I do not know the answer to this question and have been unable to find any considerable series where this form of therapy was really investigated.

So, in summary, I have talked on something about which I know very little but in preparing this talk, I have learned much that can be of great personal profit.

MODERATOR SCOTT: It is well to emphasize that many of the reports that we see in the literature are clinical evaluations and lack histologic substantiation. We never can be exactly sure (a) whether this is the correct diagnosis or (b) what would have been the natural course of this disease had we done nothing whatever. So in any clinical evaluation it is extremely difficult to say exactly what has happened as the result of administration of hormones. After figuratively using a chisel to remove some of these fibrous bands and adhesions, it is difficult for me to conceive that hormones will dissolve all these fibrotic structures in the pelvis.

Dr. Arthur Greeley will now discuss the surgical aspects, the indications for surgery and the various types of surgical treatment.

DR. ARTHUR V. GREELEY: At the 1925 meeting of the American Gynecological Society the program included a "Symposium on Misplaced Endometrial Tissue". In those papers there was little devoted to treatment. In the first paper, entitled "Relationship of Ectopic Adenomyomata to the Ovarian Function", Dr. William Graves of Boston attempted to prove, and quite successfully too, something which was then disputed but which is now well accepted,—namely, that continued activity on the part of ectopic endometrium is dependent on functioning ovarian tissue. As a result of this Graves made a plea for the treatment of rectovaginal adenomyomata by removal of all ovarian tissue. In the second paper Dr. Keene of Philadelphia described two cases in which "intense bladder symptoms were produced by endometrial invasion of the bladder wall". "Relief of symptoms and restoration of the bladder to normal followed upon removal of both ovaries, showing that excision of the affected area in the bladder is unnecessary."

Dr. Danforth of Evanston reported a case of adenomyomata of the

abdominal wall following cesarean section.

Dr. Heany of Chicago also wrote on "Adenomas of Endometrial Origin in the Laparotomy Scars Following Incision of the Pregnant Uterus".

To complete the Symposium, Dr. Sampson read a paper entitled "Heterotopic or Misplaced Endometrial Tissue" which was devoted entirely to a discussion of the origin of this condition. In the discussion, however, he was asked to say something about treatment, and stated:

> "In regard to the treatment of extensive intestinal lesions I have resected two sigmoids for this condition. The first one was diagnosed as a cancer of the sigmoid. Fortunately, the patient recovered. Four years ago I encountered another case in which there was a partial obstruction of the sigmoid which I recognized as an endometrial condition. I did not know quite how to handle it then and resected the sigmoid besides removing the uterus and the tubes and ovaries. That patient also fortunately recovered. My present reaction is not to disturb intestinal lesions except those in the appendix and epiploic appendages, and I like to remove these for histologic study and do not believe I am injuring the patient.
>
> "Dr. Heany was asked about conservative surgery in the treatment of these cases. The majority of the small lesions are of only histologic importance, are not doing the patient a bit of harm, and may never cause any trouble. I believe we can safely do conservative surgery in young women when the disease is not extensive especially if they are anxious to have children."

There is, I believe, very little change in our feeling regarding surgery for endometriosis except in the younger women with bowel involvement. With the advent of antibiotic therapy bowel resections can be performed with little risk so that conservative treatment can be carried out even in this group.

There are two important considerations to be borne in mind in the treatment of this condition. The first is one which applies to the treatment of any surgical condition but is even more important here, namely, that each case must be individualized. The second is that there is a large group of women in whom the diagnosis is not made until the abdomen is opened.

TABLE I—SURGERY NOT INDICATED

A. Older Age Group—40 Plus With Minimal Symptoms.

B. Younger Group 20—40 Years.

1) Minimal Disease and Symptoms—Fertility Not a Problem.

2) Disease More Extensive But Pregnancy Has Not Been Attempted.

A quick review of indications and surgical methods is in order. There are many patients for whom surgery is not indicated and there will be many patients in this group in whom the diagnosis is only presumptive since surgical exploration is almost necessary to establish the diagnosis (Table I).

The first group includes women who may have quite extensive disease or obvious recurrence following conservative surgery but whose symptoms are not severe enough to make surgery necessary (nor estrogen).

In younger women there are two groups in which surgery is not indicated,—namely, those in whom the extent of disease and symptoms are minimal and fertility is not a problem; and the second group in which the disease is more extensive,—six months or a year might be allowed for them to attempt to become pregnant. It is obvious that in this entire group there should be a very close follow-up in order to detect any progressive extension of the disease process.

In Table II we have the general indications for surgery—pain, which includes dysmenorrhea and dyspareunia, sterility—a complete sterility study of the patient and husband should first be carried out. One will occasionally see a young unmarried patient with extensive involvement, almost the frozen pelvis type, where surgery is indicated, even without any appreciable symptoms. Surgery is obviously indicated where the disease is becoming more extensive or the symptoms are becoming more severe. A small group of patients may have periodic bowel obstruction as the presenting symptom. These divide themselves into three groups: the first includes those with large bowel obstruction. I personally have never seen such a patient and I believe that they are rare because in most instances treatment would have been instituted long

TABLE II—INDICATIONS FOR SURGERY

I. Pain.
II. Sterility
III. Extent of Disease.
IV. Progression of Disease.
V. Bowel Obstruction.

TABLE III—CONSERVATIVE SURGERY—WITH PRESERVATION OF OVARIAN FUNCTION

I.	Indications.
	A. Child Bearing.
	B. Psychological or Emotional.
II.	Methods.
	A. Vaginal Approach.
	B. Abdominal Approach.
	C. Bowel Resection.
	D. Cauterization or Fulguration.
III.	Complications.
	A. Bowel Obstruction.
	B. Recurrence.
	C. Infection.

before they reached this stage. The second group includes those with small bowel obstructions due to endometriomas in the terminal ileum. The general surgeons see most of these cases. There is also a third group in which the small bowel becomes obstructed as a result of its adhesion to pelvic endometriosis. This may occur either *de novo* or as a result of previous surgery.

Next, we should consider conservative surgery (Table III.) I use the terms "conservative" and "radical" advisedly—mainly for want of better terms. The chief consideration, of course, is preservation of childbearing function. There is also a small group in which emotional factors may make it important to preserve ovarian function.

TABLE IV—RADICAL SURGERY—REMOVAL OF ALL OVARIAN TISSUE

I. Indications.
   A. Failure of Conservative Surgery.
   B. Older Age Group.

II. Effect on Endometrial Implants.

III. Complications.
   A. Technical Difficulties.
   B. Estrogenic Therapy.
   C. Emotional.

Regarding surgical methods, in some clinics a large percentage of patients are treated surgically by the vaginal approach. Personally, I prefer this method only for those who have a single endometrial involvement of the uterosacral ligaments or the rectovaginal septum but with no evidence of any rectal involvement.

The abdominal approach is the one most commonly used and may be either through a Pfannenstiel or a low mid-line incision, depending on the operation to be done. Through these approaches endometrial cysts on the ovaries can be resected, the pelvic structures completely explored and implants removed.

That group of patients with extensive involvement of the rectosigmoid, in whom preservation of the ovaries is important, probably constitutes the most controversial group. As I have already indicated, I believe that these women should be treated by bowel resection. The use of the cautery or fulguration is, I believe, a valuable method for destroying small superficial implants. Great care must be taken to protect uterus, bowel and large vessels when using this method. I have also used short wave fulguration in treating implants in the posterior vaginal wall.

Because of the production of raw surfaces in the cul de sac and the posterior aspect of the broad ligaments, great care must be taken to prevent small bowel adhesions by covering those areas with the rectosigmoid or the omentum. From this point of view it would seem best not to suspend the uterus. However, there are some who feel that uterine suspension is an important adjunct to surgery in order to prevent

recurrences. Other complications should also be mentioned—postoperative adhesions and bowel obstruction. Recurrence of disease, however, is probably the most common complication after conservative surgery. Smith, in 1929, stated that in his series 32.5 per cent of patients were not cured and a second operation was necessary in 9.3 per cent.

Infection may be an early postoperative complication particularly when any bowel surgery has been performed. This, however, is not often a serious one with the antibiotic therapy now available. Radical surgery with removal of all ovarian tissue should be reserved for patients in whom conservative surgery has failed or the disease has recurred, and for women in the older age group where childbearing need not be considered (Table IV).

This method invariably produces complete atrophy of endometrial implants and cure of disease even in cases when there has been complete bowel obstruction.

There may be some technical difficulties associated with complete removal of the ovaries where they are densely adherent to surrounding structures, and this may account for failure to cure some patients. These cases can usually be cured by x-ray castration. It is obvious that estrogenic therapy should not be used in this group of patients because of the danger of reactivating the endometriosis. One should also consider the emotional factors resulting from castration which have already been mentioned in connection with contraindications to surgery.

In summary:

I. Surgery is not necessary in all cases of endometriosis.
II. Conservative treatment with preservation of childbearing functions is our primary purpose.
III. Radical surgery is more or less a last resort.

MODERATOR SCOTT: We should emphasize the fact that procrastination, simple medications, watchful waiting, but close follow-up should be the plan of management in a considerable majority of these individuals.

I suspect that if we were able to do serial sections of the pelvis of all women who have had an open tube and a uterus, say at the age of 40, we would find endometriosis microscopically in every one of them. It is something which happens to the human female, and is related to her patent tubes and cyclic menses. She has become predisposed to the development of this disease.

I have rather more strict criteria before advising surgery. I would like to ask Dr. Greeley one question before we take questions from the floor. *Consider a hypothetical woman, 27 years of age, with a history of three years' infertility. We have investigated her and the husband by all approved methods. We find that she has some beading and thickening in the cul de sac, what would you advise in such a case?*

DR. GREELEY: I would advise surgery.

MODERATOR SCOTT: *How about the other members of the panel? How do they feel about it?*

DR. HELLMAN: I agree.

DR. BUXTON: I would culdoscope her.

DR. JAVERT: I would agree with that, culdoscope her.

MODERATOR SCOTT: I am not sure that I would agree with Doctors Greeley and Hellman. I feel there is no mechanical disorder and that the ovaries are free, apparently uninvolved. The point at which I would interfere is when that ovary begins to be glued down to the endometriosis in the cul-de-sac. I am one step ahead of you in the extent of the disease before I do surgery. Unless I am persuaded, by what I can feel on palpation, that it is enough of a mechanical factor I don't operate. (I say this with tongue in cheek and with some hesitancy because the last patient on whom I did a laparotomy for dysmenorrhea and only a suspicion of endometriosis, had a much more extensive involvement than my examination had led me to believe.)

DR. GREELEY: I culdoscoped a patient like that and the culdoscope went into the ovary.

CHAIRMAN GAUSE: I have seen many cases that Dr. Greeley operated on for just this situation and have often wondered why the women got pregnant.

MODERATOR SCOTT: I don't know either.

Another thing that will persuade me to resort to surgery somewhat more quickly is the presence of severe dysmenorrhea because one can combine conservative surgery with presacral neurectomy. The question of the benefits of surgery when infertility is the problem is extremely difficult to answer for the simple reason that we have no controls of an equal number of women who have the same extent of the disease but have not had surgery. How are we going to know the extent of the disease unless we look in? Nevertheless, it is my impression that most of them benefit from surgery.

DR. GREELEY: I am not convinced that their sterility has a mechanical basis. I don't think there is too much correlation between the extent of the disease, the location of the disease and the sterility. Sterility may be present in patients who have just a single implant of endometriosis in the rectovaginal septum.

MODERATOR SCOTT: Some are not infertile.

DR. GREELEY: That is correct. I am not convinced one way or another. I don't think that we know why some women with endometriosis are infertile.

MODERATOR SCOTT: *A few questions have been submitted for answer by the panel. I shall ask Dr. Greeley to begin with the subject barely mentioned here—to discuss the indications for presacral neurectomy in conjunction with conservative surgery for endometriosis.*

DR. GREELEY: I have really had no experience with presacral neurectomy in the treatment of endometriosis. I have never been very enthusiastic about the operation and I have not been convinced that it can have very much benefit in effecting a cure in those who have endometriosis. I think the important thing is to destroy all the accessible extrauterine endometrial tissue that the patient has and that is about all one can do. I should be very pleased to have someone who has had more experience with this procedure talk about it, however.

MODERATOR SCOTT: What is the experience of the panel with presacral nerve section in the treatment of endometriosis when the primary indication is pain? I have been more pleased with presacral neurectomy than you apparently have. I frequently do a presacral neurectomy in conjunction with the operation for endometriosis, using as the indication for the procedure the presence of rather severe dysmenorrhea. Results have been good in well over 80 per cent of the patients so treated. It is rather remarkable that when these women do conceive and go into labor they have no pain until the end of the first stage, usually not until the pudendal nerve branches are beginning to be impinged upon. So they have to be warned about the absence of pain during the first stage of labor.

I have not done ovarian nerve resection. Dr. Cooke advised it. It has been my personal feeling that ovarian nerve resection is unnecessary. By and large the ovarian lesions produce the fewest symptoms. One of our residents was interested in tying off the infundibulo-pelvic ligament in order to interfere with the nerve supply of the ovary. In

three of seven patients that he so treated, subsequent surgery was necessary for the removal of ovarian cysts.

MODERATOR SCOTT: *Dr. Javert, will you answer the questions addressed to you?*

DR. JAVERT: Fortunately I have only two. Before answering them I think one point that has not yet been brought up should be mentioned. The best treatment for endometriosis is pregnancy. I mention it because you said that all women 40 or more years of age, if serially sectioned, would show endometriosis. I doubt that, if they have had ten or twelve children. We must mention the inhibitory effect on these lesions and on the endometrium itself of chorionic gonadotropic hormone.

I liked the slide which referred to difficulties with pathologists. As you well know, the clinician takes a small piece of tissue and often becomes annoyed when the pathologist does not give him a diagnosis of endometriosis. As you also know, the tissue committees of some hospitals in this area refuse to accept the surgeon's clinical judgment on this matter and I think that is wrong. The surgeon was there. He saw the gross lesion. Whether the pathologist can find the characteristic tissue in the often meager amount of material submitted to the laboratory is another matter. I believe we ought to accept the surgeon's diagnosis and not depend on the pathologist's being able to find stroma or glands or both.

This questioner asks: Has it been your experience seldom to find endometriosis in Negro patients?

In our limited material at New York Hospital with a Negro population of 5 per cent, it is my recollection that we had a fair amount of endometriosis in Negroes, and have not considered it as a rarity. As a matter of fact, we had a Negro intern who insisted that it was an uncommon disease in the Negro patient. When we were able to show him six cases in a short time, he promptly changed his opinion.

Another question is as follows: Are you willing to extend the theory of lymphatic spread of non-neoplastic endometrium to such instances as endometriosis of pelvic lymph nodes found in the fetuses, infants and prepuberal girls and to the decidual reaction of pelvic lymph nodes especially in or near the subcapsular sinues in pregnant women? If not, what alternative can you propose, bearing in mind that these observations are morphologically identical with those in women from

20 to 45, which you have illustrated?

I don't know who it is that asks this question. If he has slides showing endometriosis in pelvic nodes in fetuses I would like to see them because I have never seen such material. I have not seen endometriosis in lymph nodes of infants or in girls before puberty. In a few postpuberal girls whom we studied, some 13 cases showed these lesions in the pelvic nodes. As a matter of fact, Wertheim, in 1912, was upset when his pathologists called these lesions metastatic adenocarcinomas! For many years that view had considerable vogue, so much so that when Sampson went to Europe to study they showed him such lymph nodes. He saw a good many of them, yet closed his mind's eye to them because in those days he was busy advocating the implantation theory. He did not like to "buy" anybody else's views, it seemed. He did not accept Halban's concept at all. At least he so expressed himself to Dr. N. C. Foote who also showed him a node with endometriosis.

You have not seen these lesions, Dr. Baisley?

DR. BAISLEY: No.

MODERATOR SCOTT: There was one report of apparent adenomyosis in a fetus. It is rather interesting to go back to that report of Robert Meyer. At that time he was apparently looking at and calling the remnants of the Wolffian duct in the uterine wall adenomyosis. He corrected this error subsequently. So, to my knowledge there are no instances of endometriosis in fetuses or in individuals prior to the age of menarche.

There is one at the age of 12 that I know of.

DR. WILLIAM B. OBER: I am the one who posed the question. If, at autopsy you dissect very carefully the pelvic lymph nodes of fetuses, infants, and prepuberal girls and take enough sections, you can find little inclusions of columnar epithelium surrounded by a certain amount of stroma which looks very similar to endometrial stroma, quite distinct from lymphoid tissue, and usually located in the subcapsular sinus. If you autopsy a sufficient number of pregnant women who die during the last trimester, you can find small foci of decidual transformation located chiefly near the subcapsular sinus and along the trabeculae which traverse the substance of the node. They are morphologically identical with the structures which have been described as endometriosis of pelvic lymph nodes in cases from Wertheim hysterectomies and in cases of extensive pelvic endometriosis.

It is my theory, and I advance this with some diffidence, that these represent structures which are included in the organogenesis of lymph nodes, and don't represent anything in the nature of embolic spread. I don't think they are associated with any lymphatic permeation; they are probably merely inclusions of moderately well differentiated, reasonably matured celomic mesothelium with a small amount of sub-celomic mesenchyme which under appropriate conditions of endocrine stimulation can manifest these stigmata of the endocrine response to sensitization by estrogen and further stimulation by progesterone.

MODERATOR SCOTT: We know the pelvic tissues, sub-endothelial structures in the pelvis, will respond to the hormones of pregnancy and produce a decidual reaction. I don't believe any of us consider this endometriosis *per se*. It is a response of those sub-endothelial, mesenchymal tissues. I don't know, I should very much like to see some of those sections if I could and I know that Dr. Javert would too.

DR. OBER: All these tissues are essentially derived from one parent tissue.

MODERATOR SCOTT: That is the celomic metaplasia theory. I am glad we have someone to challenge us here tonight because unfortunately the members of the panel have all been on one side. We need a little challenging. Apparently not everybody believes as we do.

DR. JAVERT: That is encouraging and as it should be.

MODERATOR SCOTT: With regard to the Negro question, in the two years, 1952 and 1953, when we surveyed the operating room material —and we have a fair number of Negro patients on our staff service— we found the incidence of endometriosis to be almost the same in the Negro ward patients as in the white private or staff patients. We were impressed by these findings because in the series we reported from Baltimore, the proportion was about five to one in favor of the white private patient.

I would like to ask Dr. Javert his opinion concerning a patient who had a ruptured appendix at the age of 16, had a drain inserted into a McBurney incision and the appendix was not removed. At the age of 20 the scar enlarged very rapidly over a period of two months. It was removed and showed endometriosis with the decidual reaction. How did that endometrium get there?

DR. JAVERT: I would suspect Sampson's implantation theory in this instance.

MODERATOR SCOTT: *In the end of the tube?*

DR. JAVERT: Perhaps.

MODERATOR SCOTT: We went back and examined the history for details as to the date of this woman's last menstrual period. We thought she might have been menstruating at the time the pelvic examination was done preoperatively, and that there could have been transplantation of endometrium. Unfortunately the record was not that complete. We had another unusual instance of endometriosis in a cholecystectomy scar, which mystified me. The patient solved the problem for us about two years later when she developed endometriosis in an old cesarean section scar. The cholecystectomy incision had been continuous with the upper portion of the cesarean section scar. The tissue was probably surgically transplanted from one scar to another.

Dr. Hellman, do you have some questions?

DR. HELLMAN: I think the question of Negro versus white is of special interest to us in view of what Dr. Scott and Dr. Javert report. We have about 75 per cent Negro patients at the Kings County Hospital and these individuals represent a population very similar to the one we saw in Baltimore and adenomyosis is quite common. Endometriosis is rare and certainly endometriosis with symptoms is extremely rare among this group of people. Whether this is due to the high fertility of the group of patients, or to the high incidence of pelvic inflammatory disease, or to a racially oriented factor, I do not know. But I suspect that it may be the first two and not the last.

There is some question about the use of male hormone. I think that, if the total dosage does not exceed 300 mg. or less per menstrual cycle, there will be no serious adverse effects. This is usually given hypodermically, during the first three weeks of the cycle, using 150 to 200 mg. during that time and the balance is given orally in a dosage of about 10 mg. a day. If one is careful and watches for increased hair growth, acne and voice changes, I think these undesired side reactions can be pretty well controlled. When this dosage level is exceeded there may be some rather unpleasant complications.

There is a question here on pregnancy which Dr. Javert passed to me. I believe our Moderator once wrote a paper on this subject, endometriosis in pregnancy. I would rather give this to him.

MODERATOR SCOTT: *Does pregnancy always cause reduction in size of cul-de-sac and uterosacral lesions? There was also another similar*

question with regard to what happens during pregnancy.

Because there is no cyclic withdrawal of progesterone, the levels of estrogen and progesterone are constant, the lesions asymptomatic. They do not grow or spread. From one point of view, they do not grow but from another point of view they *do* grow in that there is an initial swelling during the first two or three months of gestation probably due to the presence of decidual reaction, much as in the case Dr. Javert cited, in which the lesion in the lung became evident by x-ray because of the enlargement with a decidual reaction. We have followed patients with cul de sac endometriosis, have felt the lesions grow very definitely in the early months of pregnancy, but then shrink somewhat and certainly soften later on during the pregnancy. Except for the occasional rupture from the tearing of an old endometrial cyst the lesions are asymptomatic during pregnancy. Subsequent to pregnancy these lesions do not return to their full-blown symptomatic state and rapid progression, until two, three, four or five years later. I agree with Dr. Javert that if you want to protect your patients, from the prophylactic point of view, against the ravages of external endometriosis you can tell them to stay in a constant state of pregnancy! That would be a little hard on the family situation but I believe it would afford protection.

Dr. Buxton, do you have some questions to answer?

DR. BUXTON: Either keep them in a constant state of pregnancy or a constant state of lactation, one or the other!

I have a few questions here in connection with culdoscopy. One asks: How safe is culdoscopy in the face of endometriosis? The other is: What experience has the panel had with culdoscopy, etc.?

Any culdoscopic procedure carries a certain calculated risk of running into adhesions of one kind or another. The technique of doing a culdoscopy in the knee-chest position is such that if there are adhesions, say, between the intestine and the peritoneal surface of the cul-de-sac, when the trochar pierces the posterior vaginal fornix the peritoneal surface of the cul-de-sac is drawn far enough away by the adhesions so that the trochar is almost invariably apt to end up in the areolar tissue between the vaginal mucous membrane of the posterior fornix and the peritoneal surface of the pouch of Douglas. I think that some of our so-called failures occur because the culdoscope does not enter the peritoneal cavity. This failure to enter the peritoneal

cavity may well represent and be caused by some kind of pelvic peritoneal adhesions which are part of the pathology for which we are looking.

I know of several cases in which the intestine has been entered with the culdoscope and I know of no instances where it has produced any subsequent damage whatever. Apparently the artificial fistula which is created closes up rapidly and does not produce any permanent damage. Entering the intestine with the culdoscope seems to be rare. The only cases that I know of have proved so innocuous that I do not have any particular apprehensions in connection with this possibility.

Culdoscopy gives us a great deal of valuable information and is most helpful in making a diagnosis of endometriosis as well as various other types of pelvic pathology and I think it is a very useful procedure.

MODERATOR SCOTT: *You mean that the brownish material that we are looking at may not always be endometriosis?*

DR. BUXTON: It could be something else.

MODERATOR SCOTT: There is one situation in which culdoscopy is especially helpful. I refer to its use in the patient who has no palpable lesion in the pelvis but complains of pelvic pain. The symptoms may mimic what the text-books describe as the symptoms of endometriosis —although I believe that is open to question, since approximately 26 per cent of those with endometriosis have no pain or dysmenorrhea. However, if the history and symptoms suggest endometriosis, yet the nodules cannot be palpated, then, in order to make a differential diagnosis, there is a valid reason for doing culdoscopy.

We have one final question. I regret that we have not had time to cover all the questions submitted. The questioner quotes Dr. Gardner of Chicago as saying: "All nodules larger than 1 to 2 cm. in diameter, and presumed to be endometriosis, in the cul-de-sac should be biopsied in order to rule out a possible malignancy." Please comment!

We have not mentioned at any time during this meeting one of the major reasons for surgery. The diagnosis of a cystic or nodular ovarian lesion in the pelvis as endometriosis remains only a clinical impression until confirmed by surgery and microscopic examination. The lesion can be carcinoma and the implants in the cul-de-sac can be carcinoma. Where there is no appreciable enlargement of the ovaries, I do not agree with the injunction to biopsy all 1 to 2 cm. nodules found in the cul-de-sac. I think I would have to do a complete reshuffling of my

follow-up practice of patients with this size nodule in the cul-de-sac that I have been following for years and admit them all to the hospital for biopsy. I really don't believe that I am going to find that I have done entirely wrong by following and watching such nodules. But I do become worried when I feel the nodules together with an enlargement of the ovary or if there is an unusually rapid growth of the nodules in the cul-de-sac or an unusually rapid enlargement of the ovary in association with the nodules. Then we must suspect malignancy and our main reason for surgery in many of these instances may be to exclude malignancy rather than to treat symptoms.

We are at the end of our time. I am sorry we have not had time to answer all the questions. I want to thank the panel members and I want to thank you all for your kind attention.

MANAGEMENT OF ACUTE RENAL FAILURE COMPLICATING MASSIVE TRAUMA*

SAMUEL R. POWERS, JR., JOHN KILEY and ANTONIO BOBA†

ACUTE renal tubular degeneration as a late complication of massive trauma is increasing in frequency. An important factor in this increased incidence is the striking improvement in resuscitative measures which are now generally available and permit a significant number of severely injured patients to survive long enough to develop renal complications. The prevalence of this condition was demonstrated during World War II when 40 per cent of a group of battle casualties which required 15 or more pints of blood for resuscitation developed acute renal failure with a 90 per cent mortality rate[1]. Early diagnosis, followed by adequate surgical and medical therapy, can probably reduce this mortality figure to 50 per cent or less. This report will present the program of management practiced by our renal failure team and will offer some recent experimental data on the pathogenesis and possible prevention of this syndrome.

The early diagnosis of impending renal tubular damage is based on the recognition of diminished urine volume. Oliguria is arbitrarily defined as a 24 hour urine volume below 400 ml. or, in a more practical sense, under 15 ml. per hour. A correct diagnosis of renal tubular damage cannot, however, be made solely on the basis of oliguria since the dehydration which accompanies large crush injuries will limit urine output. This dehydration results principally from the sequestration of large unmeasurable volumes of extracellular fluid into the crushed tissues and makes any arbitrary rule as to fluid requirement impossible. Since the therapy of dehydration oliguria and of renal shutdown are diametrically opposed, it is essential that this distinction be made as early as possible. In this regard, it is helpful to have an indwelling urethral catheter inserted as soon as the patient is seen and to have hourly urine volumes

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recorded on the chart. Although there may be some risk of introducing infection into the urinary tract, with possible pyelonephritis as a sequela, we feel that the necessity for accurate, hour by hour information on the volume of urine output outweighs all other considerations in the severely injured patient. If the hourly volume falls below 15 ml., a decision must be made as to whether intravenous fluids should be restricted or forced. The answer to this problem depends on the over-all state of hydration of the patient, a factor which often can be assessed only by a therapeutic test. It is our practice under these circumstances to administer a solution of half normal saline in 2.5 per cent glucose at a rapid rate until either the urine volume rises or minimal signs of edema appear. Although any edema is undesirable, it may be practically impossible to rule out dehydration as a cause of oliguria following massive trauma without producing minimal clinical evidence of overhydration. If minimal signs of edema do develop in the absence of increased urine flow, the rate of fluid administration is sharply reduced and the therapeutic regimen for renal shutdown begun. Early, rapid rehydration will not only provide a quick diagnostic test but may possibly modify or even circumvent the clinical course of renal tubular degeneration.

The clinical picture of acute renal failure following trauma resembles, but is quantitatively different from, that associated with other types of renal failure. As a result of the crushed tissue, the NPN may rise at four times the rate and serum potassium at twice the rate for simple anuria. In addition, the increased catabolic rate which is associated with the metabolic response to injury results in an augmented rate of potassium release from uninjured tissue. We have seen the serum potassium rise 2.5 mEq./L in 24 hours in a severely injured patient.

A further complicating feature in this group of patients is the high incidence of serious infections which result from the combination of the uremia with its attendant lowering of resistance and the presence of necrotic, crushed tissue. Indeed, it is these infections, rather than uremia itself, which account for the bulk of the mortalities following renal shutdown.

The special features just discussed suggest the cardinal principles of the therapeutic program. These aim at limiting the rapid increase in blood NPN and potassium levels as well as lessening the chance for severe infection by early, radical debridement of all necrotic or crushed tissue, and also being prepared to handle the accelerated increases of

these substances by means of appropriate medical therapy or, if necessary, hemodialysis.

As soon as the diagnosis of renal tubular degeneration has become established, the rate of fluid administration must be adjusted so as to balance the rate of insensible loss. At the present time, there is no adequate method for accurately determining either the amount of fluid loss, especially in a febrile patient or the rate of catabolic, endogenous water production. There are, however, two helpful guides for assessing the water balance of the uremic patient. Most important is the daily body weight which should show a steady fall of about one pound per day. A second helpful guide is the constancy of the serum sodium. If there is no unusual loss of this ion from the gastrointestinal tract, then its concentration in the serum will reflect any change in the volume of extracellular water. In the usual crushed patient, 300-400 ml. of added water per day will suffice. It must be emphasized that the route of administration, whether by mouth or by vein, is unimportant. Pulmonary edema will develop just as surely from oral as from intravenous excess. This fluid should be given as a 50 per cent glucose solution in an effort to reduce protein catabolism as much as possible.

The rapid rise in serum potassium which follows severe trauma poses a number of special problems in management that differ sharply from the usual case of non-traumatic acute renal failure. The normal catabolic rate in uninjured anuric patients will produce a rise in the serum potassium of no more than 0.5 mEq./L in a 24 hour period, but this figure may rise to 2.0 mEq./L per day or more following extensive muscle crushing. The toxic effects of this process are accentuated if a simultaneous drop in the serum sodium is allowed to develop since the physiologic effects of high serum potassium are due in part to the ratio of this ion to other positive ions. It has been demonstrated in the dog that the electrocardiographic patterns associated with serum potassium levels as high as 8-10 mEq./L can be reversed if the serum sodium is simultaneously elevated to abnormally high levels. We do not suggest deliberate elevation of the serum sodium as a therapeutic procedure, but these studies do suggest that the maintenance of the sodium levels within normal limits may be of value.

The intravenous administration of glucose and insulin has been shown to lower temporarily the serum potassium level since potassium is utilized in the transport of glucose across the cell membrane. Unfor-

tunately, the reduction in serum potassium is of short duration and therefore the use of glucose and insulin has little place in the therapy of prolonged elevations. It is occasionally helpful as an emergency measure to protect the myocardium while the patient is being prepared for hemodialysis but should not be considered as definitive treatment. In addition, this technique has the marked disadvantage of driving the potassium into the cell where it is inaccessible for removal by dialysis.

The oral or rectal administration of exchange resins will extract potassium from the body in sufficient amounts to remove the potassium which results from normal protein catabolism. They can be considered as the definitive treatment for hyperkalemia associated with anuria in the non-traumatized patient, and will be quite adequate in the crush syndrome once the potassium load which is released from the damaged tissues has been controlled and intestinal function has resumed.

Hemodialysis is an essential therapeutic modality in the severely crushed anuric patient, both for the control of marked hyperkalemia during the first days after injury and also for the subsequent removal of nonprotein nitrogen. The indications for dialysis thus fall under two rather separate headings. Evidence of potassium and other electrolyte abnormalities as judged by serum levels, electrocardiographic changes, and skeletal muscular activity, may require dialysis within the first 72 hours of anuria. Indications for dialysis during the later period of renal shutdown are not as clear-cut and require considerable experience to evaluate. Elevation of the NPN, *per se*, is a useful guide but cannot be unreservedly accepted since following trauma, the cerebral effects of uremia will occur at lower serum NPN values than in the non-traumatized uremic individual. The most helpful clinical indication is the first evidence of disturbed psychomotor or neuromotor function expressed either as increased irritability or as somnolence. Alternate periods of depression and bursts of anger at nurses and doctors over trivial matters are ominous signs, heralding the early onset of convulsions, respiratory paralysis, and coma. One of our patients who was dialyzed on seven occasions learned to recognize the symptoms and requested that he be returned to the artificial kidney.

It is apparent that successful management requires a medical-surgical team experienced in the application of all these measures. With this combined program, the mortality for uremia following trauma has been reduced to 50 per cent in a series of 36 cases. Uncontrollable infection,

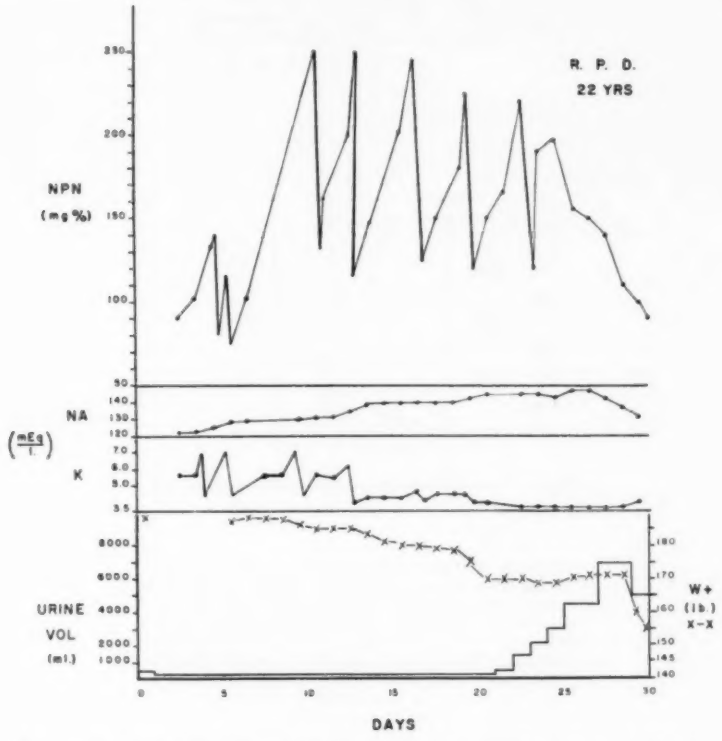

Fig. 1—Chemical data from a patient with post-traumatic acute renal failure leading to 21 days of anuria. The sharp falls in NPN coincide with the seven hemodialyses. The first three dialyses were carried out primarily for hyperkalemia. (See ref. 2. Reprinted by permission of the New York State Journal of Medicine.)

hemorrhagic diatheses, and wound healing complications were the principal causes of death.

These principles can be illustrated by a brief case report. A 22 year old truck driver was crushed beneath his overturned cab and brought to the hospital in profound shock. Because of the signs of massive intra-abdominal hemorrhage, he was taken to the operating room where emergency thoracotomy was performed because of cardiac standstill. Laparotomy was then carried out with resection of a ruptured spleen, exteriorization of the avulsed left colon, ligation of the severed inferior mesenteric vein, and ligation of the transected left common iliac vein,

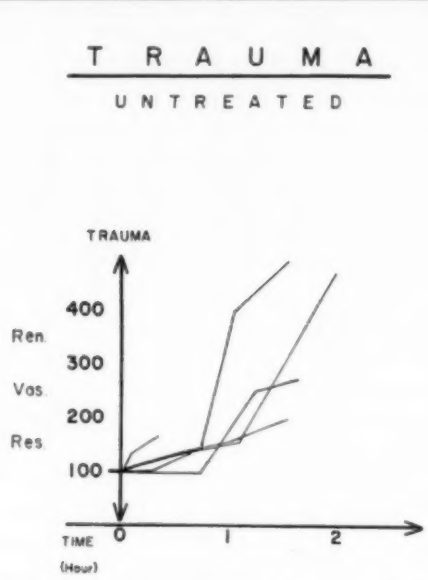

Fig. 2—Proportional changes in renal vascular resistance following mallet trauma in six animals. The control value in each case was arbitrarily taken as 100. Blood pressure in all animals remained within 10 per cent of control values. The sharp increases in renal vascular resistance indicate a proportional fall in renal blood flow.

It was noted at the time of surgery that extensive muscle crushing was present, involving the abdominal muscles, left psoas major muscle and especially the muscles of both legs, but without fracture. Sixteen hours after surgery the diagnosis of renal shutdown was established and medical therapy instituted. Figure 1 illustrates the pertinent features of the course during the succeeding 21 days of uremia. It is apparent that although the fluid intake during this period averaged only 350 ml. per day, he was overhydrated as evidenced by his final weight following diuresis. The indications for the seven separate hemodialyses are shown by the serum potassium and NPN levels. It can be seen that the first dialysis was required on the fourth post-injury day because of a serum potassium level of 7.0 mEq./L associated with marked electrocardiographic changes. His course was complicated by pneumonia, markedly retarded wound healing, and finally the development of multiple large

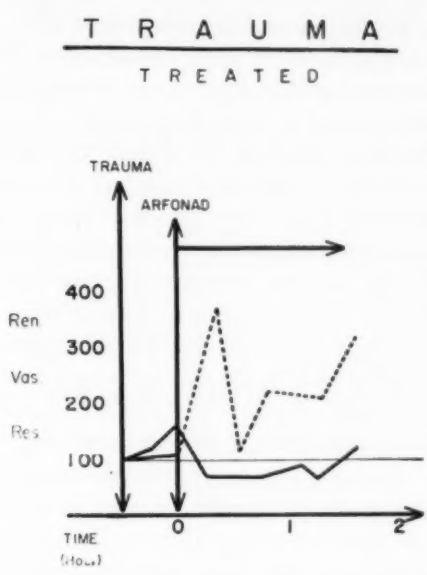

Fig. 3—Changes in renal vascular resistance resulting from the administration of Arfonad after the completion of trauma. The solid line was calculated from an animal in which the blood pressure was kept near 85 mm. Hg. The dotted line was calculated from an animal with a blood pressure which fluctuated between 30 and 60 mm. Hg. Extreme hypotension apparently produces an effective increase in renal vascular resistance (dotted line), whereas ganglionic blockade with only moderate hypotension (solid line) abolishes the effect of trauma on the renal vascular resistance.

abscesses in the crushed muscles of the thigh. It is believed that the early radical surgery, combined with frequent, properly timed hemodialysis, was an important factor in his eventual recovery. Decisions on all phases of management were made in consultation between the internist and surgeon. This case has been reported elsewhere in detail[2].

The prevention of acute renal tubular degeneration following trauma is currently under investigation and some preliminary results from animal studies are of interest. The thesis that renal tubular anoxia is an important feature in pathogenesis is generally accepted. We set out to determine whether this tubular anoxia resulted solely from the hypotension associated with shock, or whether a decrease in renal blood flow

due to a selective renal vasoconstriction independent of the systemic blood pressure, might so lower renal tubular blood flow that tubular anoxia and subsequent cellular degeneration would occur. In order to test this hypothesis, graded muscle trauma was produced in the hind leg of 36 dogs. At the same time renal blood flow was measured directly by inserting a "T" cannula in the renal vein and quantitatively diverting renal venous blood into a graduate cylinder. Figure 2 shows the results of six experiments and confirms the hypothesis that renal blood flow may decrease sharply without concurrent hypotension. It is of particular interest that five of the six animals showed histological changes of acute renal tubular degeneration at the time of sacrifice two days later.

Having established that both the pathological and physiological changes of renal tubular degeneration could be produced by muscle trauma in the intact anesthetized normotensive dog, the experiments were repeated in the same way except that the kidney was completely denervated. In this group of animals the renal blood flow remained at control levels throughout the study, indicating that the renal vasoconstriction observed in the first group was mediated through the autonomic nervous system. This last observation suggested a possible technique for the prevention of renal tubular degeneration. In a third group of animals, a ganglionic blocking drug (Arfonad) was given intravenously immediately following the trauma. Figure 3 shows that although the renal blood flow decreased, this change was proportional to the fall in systemic blood pressure and therefore the effect of trauma on the renal vascular resistance had been abolished. Histologic study of the kidney, 48 hours later, revealed no evidence of tubular degeneration in seven of eight animals studied.

This experimental work is still in a preliminary stage, but it suggests the possibility that the complex chain of disturbed physiologic events which leads to renal tubular damage may be made reversible by a combination of adequate resuscitative measures and specific pharmacologic agents.

REFERENCES

1. Ladd, M. *Battle casualties in Korea: Studies of the surgical research team, Vol. 4 Post traumatic renal insufficiency.* Washington, D. C. US Army Medical Service Graduate School, Walter Reed Army Medical Center, 1956, p. 193-233.

2. Kiley, J. E., Attarian, E., Macomber, W. B., Van Orden, P. S. and Powers, S. R. Acute renal insufficiency; hypermetabolic state developing after seven dialyses, *N. Y. St. J. Med. 58*:4065-67, 1958.

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February 13
1959

USE OF STEROIDS IN RHEUMATIC DISEASES

Moderator: CHARLES RAGAN—Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University; Associate Attending Physician, Presbyterian Hospital

Panel Members

THEODORE B. BAYLES—Research Director, the Robert Breck Brigham Hospital, Boston; Clinical Associate in Medicine, Harvard Medical School

EDWARD E. FISCHEL—Director, Department of Medicine, Bronx Hospital; Associate Clinical Professor of Medicine, Albert Einstein College of Medicine

RICHARD H. FREYBERG—Professor of Clinical Medicine, Cornell University Medical College; Director, Department of Rheumatic Diseases, Hospital for Special Surgery

FRIDAY
March 13
1959

THE USE OF CHLOROTHIAZIDE AND OTHER DIURETIC AGENTS

Moderator: JOHN H. LARAGH

FRIDAY
April 10
1959

PROPHYLACTIC USE OF ANTIBIOTICS

Moderator: PERRIN H. LONG

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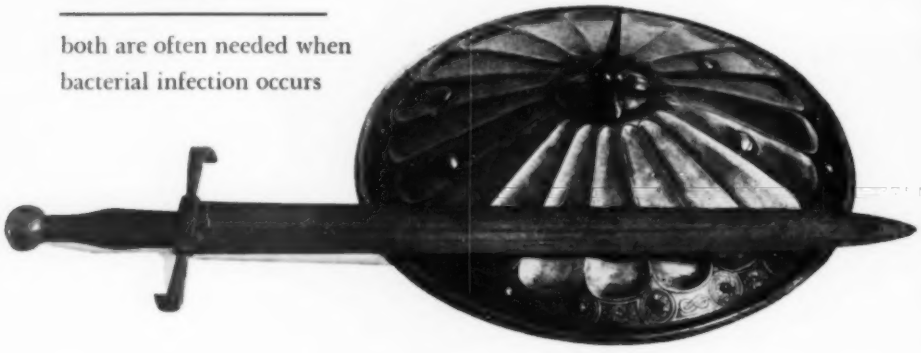

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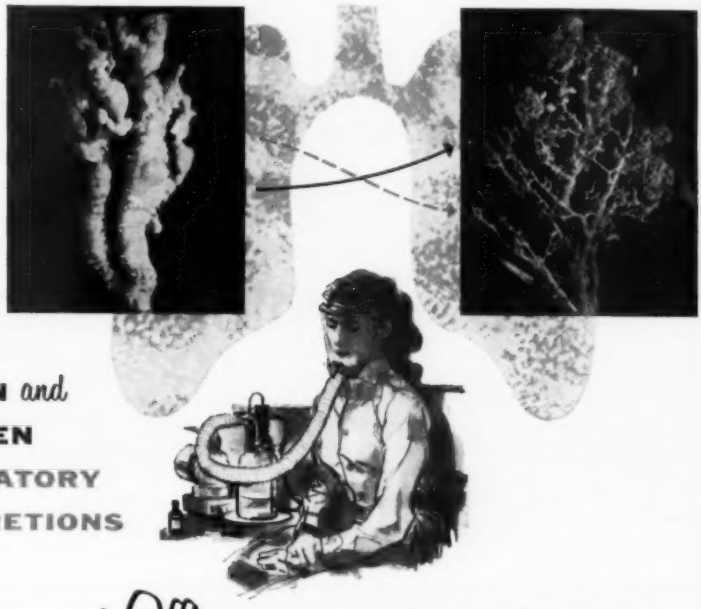

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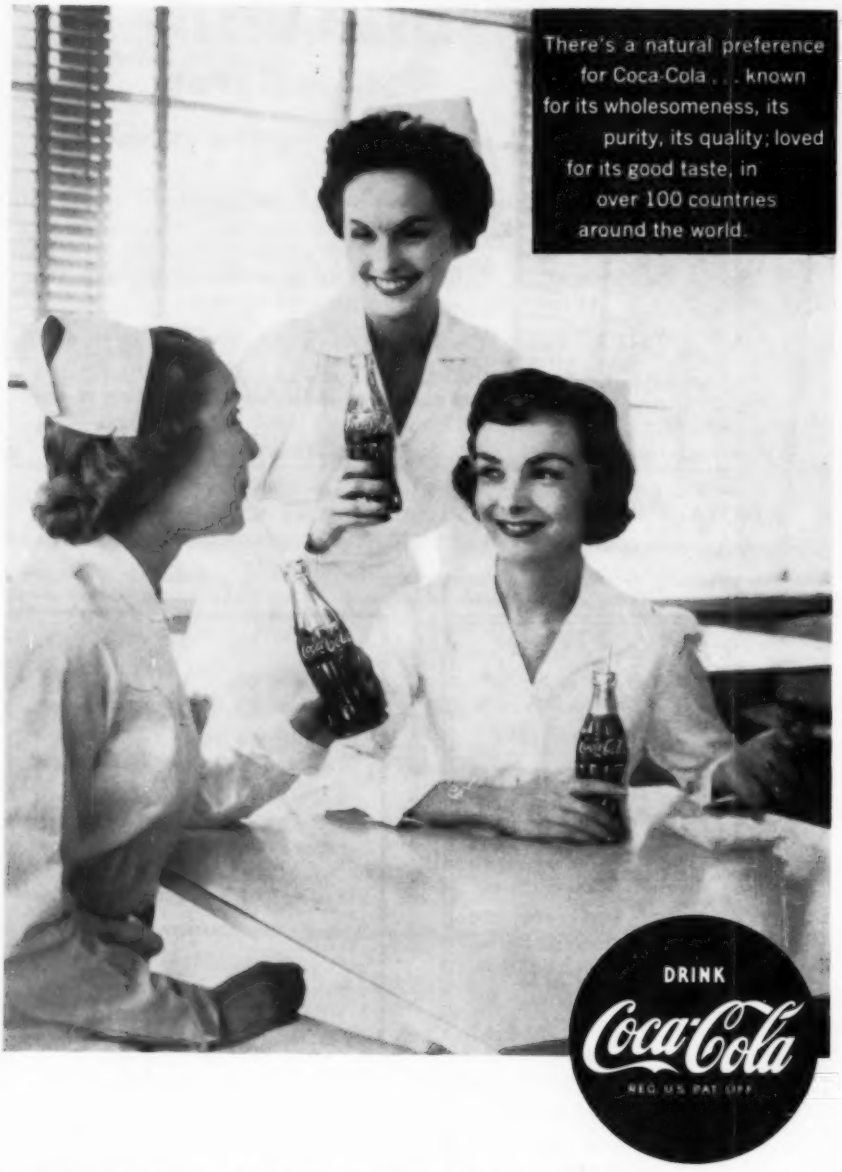

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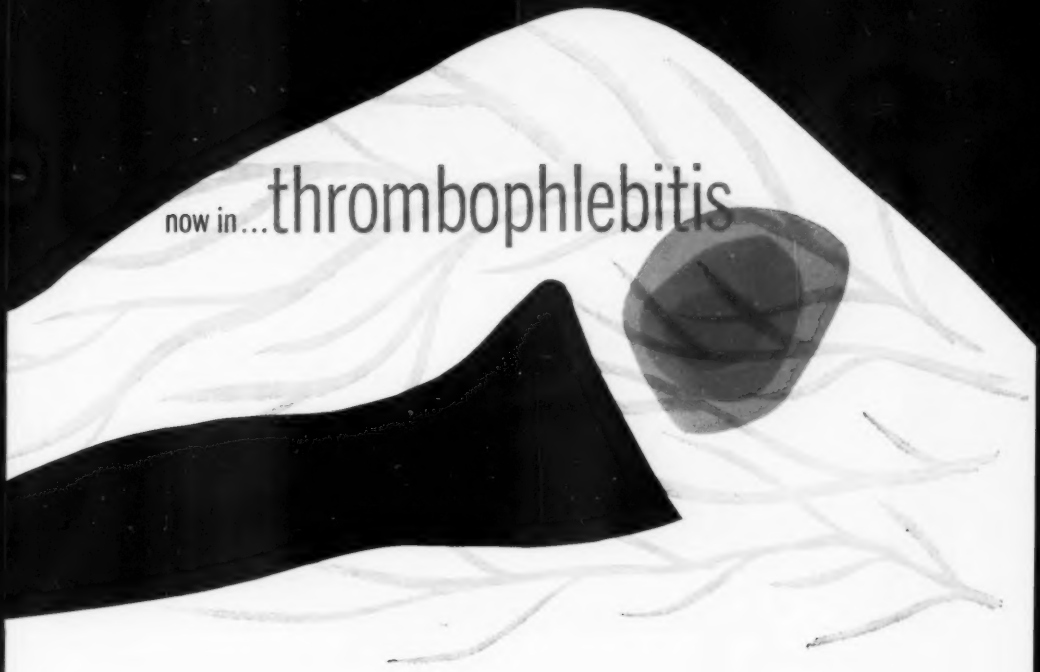

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References: (1) Stein, I. D.: Circulation 12:833, 1955. (2) Potvin, L.: Bull. Assoc. méd. lang. franç. Canada 85:941, 1956. (3) Sigg, K.: Angiology 8:44, 1957. (4) Elder, H. H. A., and Armstrong, J. B.: Practitioner 178:479, 1957. (5) Braden, F. R., Collins, C. G., and Sewell, J. W.: J. Louisiana M. Soc. 109:372, 1957.

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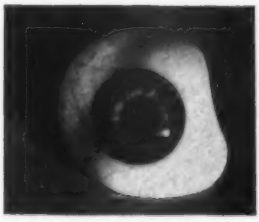

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References: 1. Alyea, E. P.: Infections and Inflammations of the Male Genital Tract, in Campbell, M.: Urology, Philadelphia, W. B. Saunders Co., 1954, vol. 1, p. 643. 2. Barnes, R. W., in discussion of Chinn, J., and Bischoff, A. J.: Tr. West. Sect. Am. Urol. Ass. 22:189, 1955. 3. Goodwin, W. E., and Turner, R. D.: Prostatitis, in Conn, F.: Current Therapy 1958, Philadelphia, W. B. Saunders Co., 1958, p. 399.

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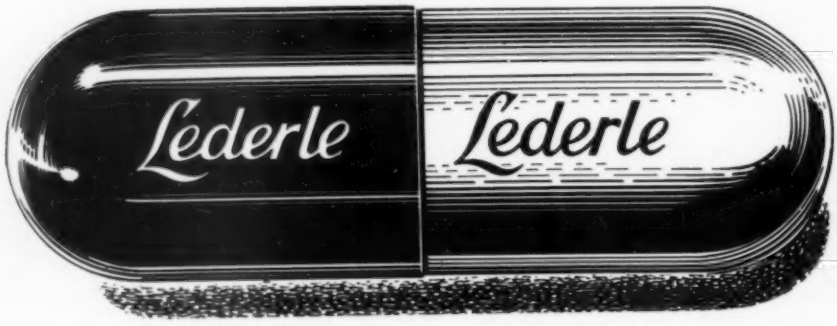

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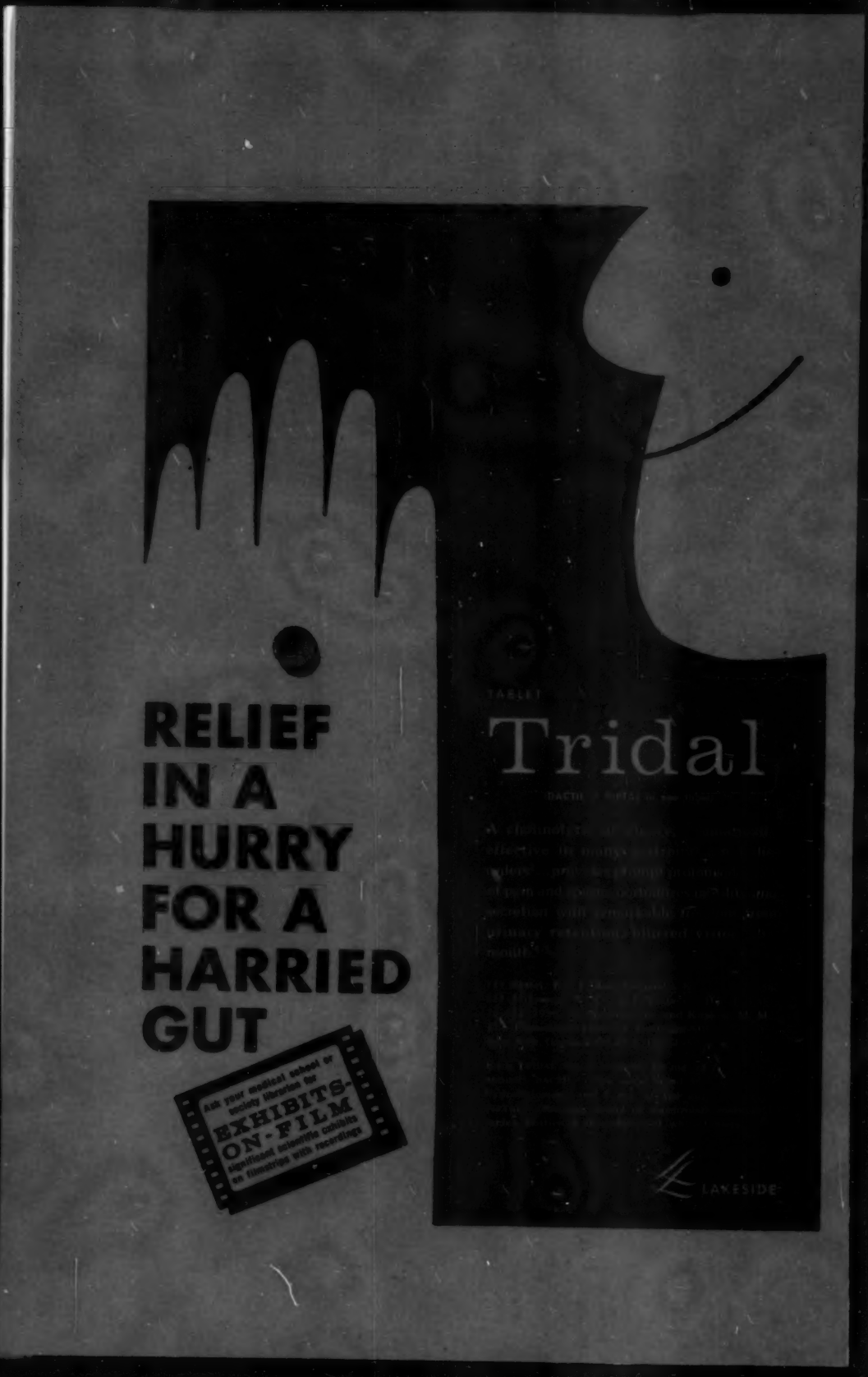
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